PRESBYTERIAN-ST. LUKE'S HOSPITAL

MEDICAL BULLETIN

VOL. 7 NO. 1 JANUARY 1968

TRAUMA SYMPOSIUM

Ski Injuries

The Motorcycle: Its Risks and Hazards

Trauma to the Urogenital System

The Management of Severe Blunt Chest Trauma

Penetrating and Non-penetrating Abdominal Wounds

Complications of Supracondylar Fracture of the Humerus

Managing Vascular Injuries of the Lower Extremity

The Editor's Page

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VOL. 7 NO. 1 JANUARY 1968

TABLE OF CONTENTS

page

2 **Ski Injuries**
FRANCIS M. HOWARD, M.D. and THOMAS MCNEILL, M.D.

9 **The Motorcycle: Its Risks and Hazards**
RICHARD G. CALDWELL, M.D.

15 **Trauma to the Urogenital System**
CHARLES F. MCKIEL, JR., M.D.

27 **The Management of Severe Blunt Chest Trauma**
L. PENFIELD FABER, M.D.

33 **Penetrating and Non-penetrating Abdominal Wounds**
ROBERT W. JAMIESON, PH.B., M.S., M.D.

40 **Complications of Supracondylar Fracture of the Humerus**
RICHARD L. JACOBS, M.D.

48 **Managing Vascular Injuries of the Lower Extremity**
ROGER L. MEHL, M.D.

55 **The Editor's Page**

SKI INJURIES

Francis M. Howard, M.D.[1]
Thomas McNeill, M.D.[2]

INTRODUCTION

The allure of skiing carries with it the beauty of a snow capped mountain, the warmth of friends, and the thrill of speed. Speed is translated to injuries. In the United States, there are *four million* skiers and the growth of the sport is increasing ten per cent each year.

Local Conditions

While the ski slope itself with its hidden rocks, sharply carved moguls, and blind spots at the end of a catwalk may be a hazard, most injuries occur in the more gentle areas which are skied more frequently and are well manicured. Avalanche injuries usually mean flagrant violations of warning signs.

The direct rays of the sun plus the reflected sunlight on the snow can combine to produce a severe sunburn of the face and eyes. Skin cream and sunglasses which shield laterally as well as filter ultraviolet rays are essentials for the mountain skier.

Equipment

The skier's equipment has five components:

1. Skis
2. Bindings
3. Poles
4. Boots
5. Apparel

The ski itself can cause injuries by lacerating a skier with the sharp edge or turn into a spear when it becomes a run-away ski, or may become the keen-edged blade of a twirling windmill as the skier tumbles downhill in a fall.

During a fall, a great torsion force is produced on the skier's leg when the ski is rigidly fixed through the intermediary of a binding and boot. It is to break this long lever arm that the so-called "safety bindings" were developed by releasing the boot from the ski either by rotating the toe out of the toepiece or by an upward and forward thrust of the heel which then disengages the heel of the boot from the ski. When the bindings fail to release, either a torsional stress around the long axis of the leg can produce an oblique fracture of the tibia or the heel can be locked so that the force is applied at the top of the ski boot causing a transverse fracture of the tibia shaft. The mechanisms and forces involved are illustrated in figures 1 and 2. These computations vary somewhat from previous estimates of the forces involved and at least, as far as spiral fractures are concerned, are within the range of preventability by proper conditioning.

Two major factors are responsible for failure of these "safety bindings" to

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release from the ski in a fall. First, the mechanism may be set too tight for the strength of the skier, such as for a woman or a child. Second, the release mechanism may be frozen as ice accumulates during a day of skiing.

The ski poles can penetrate the thorax, abdomen, or thighs or they may even cause thumb injuries to the skier when the tip of the pole gets caught in the snow and the hand or wrist twists about the grip. Furthermore, the poles can immobilize a skier's hands if the snow from an avalanche engulfs him.

In the past ten years, ski boots have changed from the handmade to the machine produced fiberglass boot with sponge rubber padding inserts. The modern boot is far superior, giving a firmer grip on the skier's leg and heel, thereby giving him greater control of the skis by transmitting motion directly to the skis. Because of this firm fit, the minor fracture of the lateral malleolus due to a twisting force on the ankle has often been supplanted by a fracture of the shaft of the tibia above the boot top.

Skier's apparel should protect against the cold and wind and may require a face mask to prevent frostbite of the face, nose, and ears. Furthermore, the apparel should fit tightly to prevent it from being caught on lift machinery or tree branches as strangulation has occurred.

Conditioning

To avoid injuries, the necessity for conditioning before the ski season and before the first run of the day cannot be over-emphasized. In "The Moveable Feast" Hemingway noted that spiral

The authors wish to thank Dr. Julia Apter and Michael Janas of the Department of Biomathematics of the Division of Surgery of Presbyterian-St. Luke's Hospital for the computations of the engineering principles involved.

Figure 1 ***(see pages 4 and 5)***

$$\sigma = \frac{W}{2} \sin\theta \frac{WV_o}{2g\triangle t} \cos\theta \pm 16{,}500 \left(W \cos\theta - \frac{WV_o}{g\triangle t} \sin\theta \right)$$

Conditions same as for Figure 2 except $\triangle t = 5$ sec.

σ_{MAX}—40,000 pounds per sq. ft.

Figure 2 ***(see pages 4 and 5)***

$$\sigma = [W\,1 - 16{,}500(\mathcal{Z} - 3)(r \sin\phi)] \left[\cos\theta - \frac{V_o}{g\triangle t} \sin\theta \right]$$

Legend

σ—Internal stress on skier's leg (pounds per square foot)
W—Weight of skier (pounds)
$\mathcal{Z}$—Distance along axis of skier's leg measured from bottom of ski (feet)
$r \sin\phi$—Distance from an imaginary plane that cuts through diameter of cross section of skier's leg

θ—Angle of the major axis which skier makes into the ground
V_o—Skier's speed at impact (feet per sec -1)
g—Local acceleration of gravity (feet per sec -2)
$\triangle t$—Time interval for skier to decelerate from V_o to Zero velocity

W—150 lbs.
$\mathcal{Z}$—6 inches
θ—1 radians
$\triangle t$—1 sec.
V_o—50 ft/sec -1

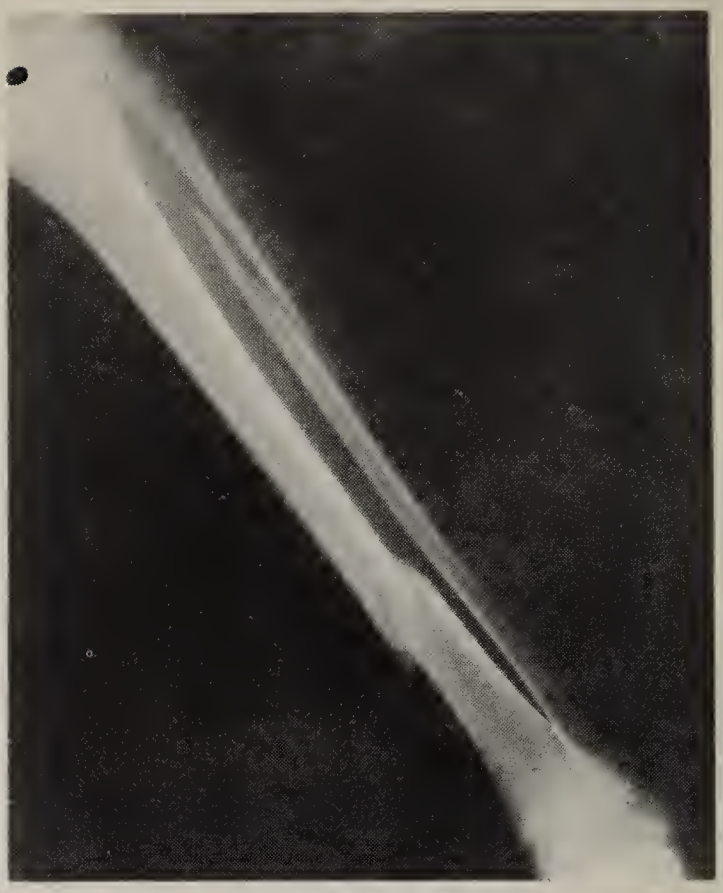

Fig. 1a—Mechanism of the ski injury (upper left)

Fig. 1b—X-ray of the spiral fracture (upper center)

Fig. 1c—Biomathematical computation of the stress force (upper right, opposite page)

Spiral Fracture:—Shows a skier incurring a spiral, oblique fracture of the shaft of the tibia and fibula. Biomathematical computations revealed a stress force much smaller than the "ski boot" type fracture, chiefly because of the factors of rotational forces. (See formula and explanation.)

Fig. 2a—Mechanism of the ski injury (lower left)

Fig. 2b—X-ray of the "Ski boot fracture" (lower center)

Fig. 2c—Biomathematical computation of the stress force (lower right, opposite page)

Ski Boot Fracture:—Demonstrates a skier incurring a transverse fracture of the tibia and fibula in the distal third of the shaft of the leg, a "ski boot fracture." If a skier of 150 pounds were traveling at about 30 miles per hour, the force at the time of fracture could equal 200,000 pounds per square foot or over 1,000 pounds per square inch.

$$\sigma = \frac{W}{2} \sin\theta - \left(\frac{V_0}{g\Delta + \cos\theta}\right) + 16{,}500$$

$$r\,W \sin\phi \quad \left(\cos\theta - \frac{V_0}{g\Delta t} \sin\theta\right)$$

$$\sigma \text{ max} = 40{,}000 \text{ lb./sq. ft.}$$

$$\sigma = W \left(1 - 16{,}500\ Z\ r \sin\phi\right)\left(\cos\theta - \frac{V_0}{g\Delta t}\sin\theta\right)$$

$$\sigma \text{ max} = 200{,}000 \text{ lb./sq. ft.}$$

fractures of the tibia were very rare among Alpine skiers due to the strong leg muscles that were developed when skiers had to climb up the mountain before the advent of the ski lift. A simple conditioning program, such as climbing two flights of stairs instead of using the elevator, swimming to increase respiratory reserve, doing calisthenics such as "push-ups," "kneebends," squatting exercises and trunk flexion can help harden the skier's muscles.

Age and Experience

Statistical studies have revealed that the accident rate is highest for skiers between the ages of sixteen and twenty-five years.

At Aspen Mountain, most accidents

occurred on easier slopes (which were also the most heavily traveled slopes) rather than on the more difficult areas, while at the Aspen Complex over 50% of the injuries occurred during the last two hours of skiing during the day, suggesting that these injuries were due either to skier fatigue or the rapidly changing ski conditions prior to sunset when the light goes flat and slopes become icy. The belief that most ski injuries occur in the late afternoon is deeply rooted in skiing lore. However, Dr. James Garrett, based on his experience at Vail, Colorado from 1964 to 1965 regards this belief as statistically erroneous due to the fact that more people are skiing at this time of day than are skiing in the morning. Garrett states that most ski injuries occur during the first two hours of individual skiing.[9]

Two of the major causes of skiing injuries are: 1) Lack of adequate professional instruction; and 2) The dangerous period of moving up from one level of skill to another, such as novice to intermediate, or intermediate to expert.

Howorth states that although 35% of the skiers are female, they account for 47% of the injuries.[7] As to skiing ability, Ellison, *et al.* state that 71% of persons injured while skiing have been skiing one year or less.[3] With proper ski instruction, this figure has been markedly reduced.

In Aspen, the injuries of male novices under the age of 30 years were 24 per thousand man days of skiing while injuries for female novices under 30 years were 17 per thousand days of skiing. With skiing experience, the accident rate drops since accidents for intermediate

TABLE I: INJURIES ACCORDING TO SKIING ABILITY[8]

	Buttermilk Mt.	Aspen Mt.
Novice	59%	15%
Intermediate	37%	58%
Expert	3%	25%

Among the chief causes of accidents were skiing beyond his ability (Buttermilk 39.4%, Aspen 28.2%) adverse snow conditions, fatigue, jumping, and racing (7%).

TABLE II: TYPES OF INJURIES

	Aspen Mt.	Buttermilk Mt.	Moritz, et al.[5]
Fractures	37%	35.5%	21.9%
Sprains	37%	43.6%	43.4%
Dislocations	5.7%	3.2%	1.8%
Lacerations	9%	7.3%	8.7%

TABLE III: TYPES OF FRACTURES (AFTER ELLISON, ET AL.)[3]

Lateral malleous	34%
Medial Malleous	8%
Tibia or tibia and fibula-shaft	37%
Bimalleolar	5%
Fibular shaft	1%
Foot	2%
Femur	0.4%
Upper extremity	8%

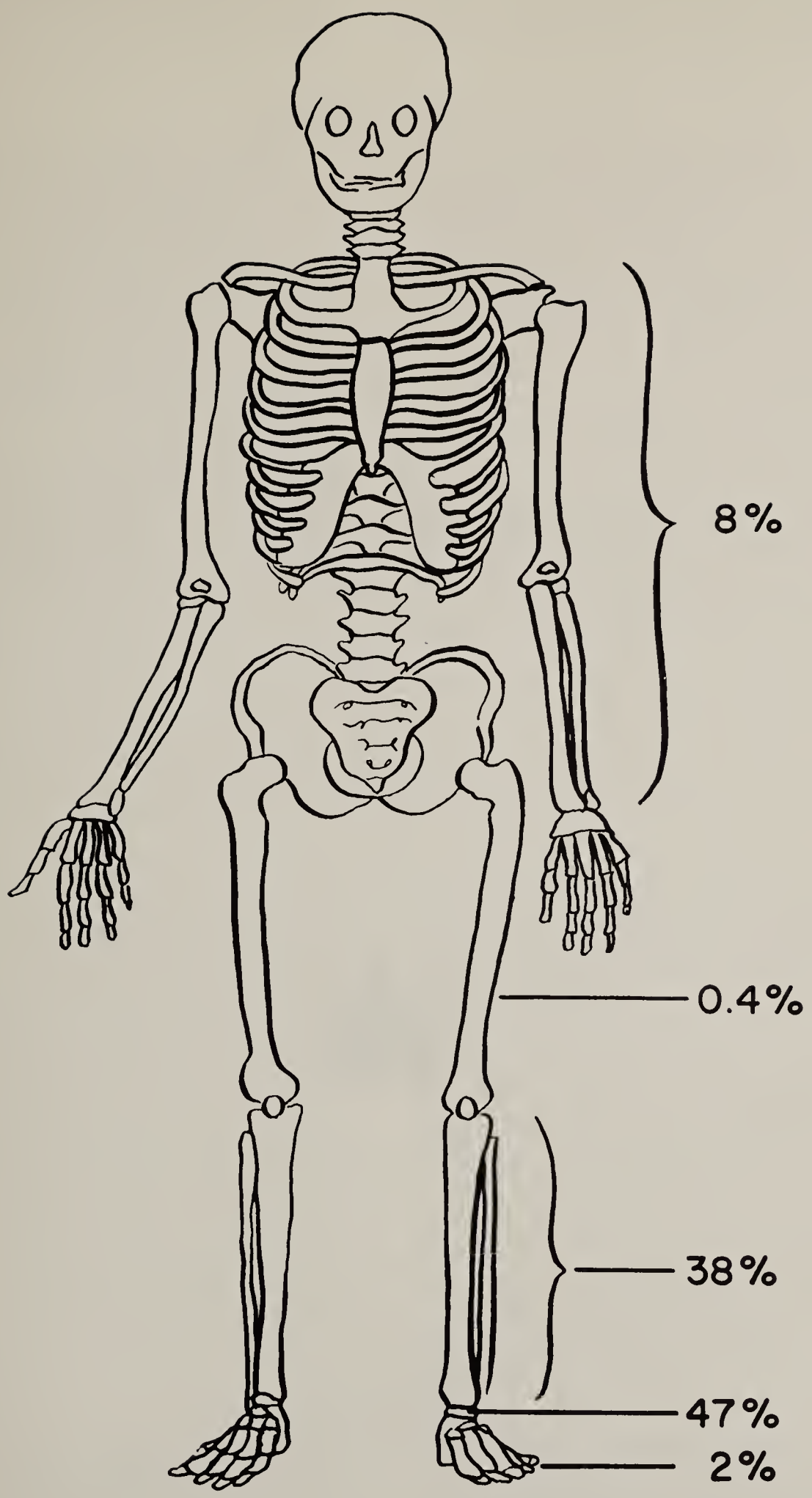

Fig. 3—Location of Fractures (after Ellison, et al.)[3]

and expert skiers were 6 per thousand days of skiing of both sexes. If a person has passed the age of 30 years and has been skiing for five years, his chance of injury is considerably less than this latter figure.

CONCLUSIONS

Skiing has no higher injury rate per one thousand man days of participation than soccer, ice hockey or American football. Furthermore, it would appear that the current rate of injury could be greatly reduced if:

1. Adequate professional ski instruction is obtained.
2. Safety release bindings are carefully adjusted for women and children skiers and are checked for ice.
3. Skiers exercise greater caution when beginning to ski at a level higher than their previous skill.
4. Skiers would develop a muscle conditioning program prior to the season and especially before the first two hours of skiing. These exercises should especially be aimed at strengthening the ankles, knees and legs since the bulk of injuries occur at these sites.
5. Lifts would close before dangerous conditions, such as flat light or ice develop.

The thrilling appeal of skiing comes from a sport that is intrinsically dangerous due to its speed, but with proper caution it can be enjoyed without the skier becoming a statistical casualty.

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THE MOTORCYCLE: ITS RISKS AND HAZARDS

Richard G. Caldwell, M.D.[1]

INTRODUCTION

In the past five to ten years the two-wheeled motor vehicle has become an ever-increasing attraction to the American people. Registration of all motor vehicles in the United States, according to the National Safety Council, has risen 26% since 1961, with a corresponding increase in motorcycle registration of 220%. An increase of 210% in the death rate has similarly been recorded for the motorcyclist. This 210% can best be graphically represented when it is broken down into yearly increments. With the exception of 1961 there has been a steady percentage rise in the yearly death rate (Figure I).

Registration-death statistics have little significance when compared against themselves; therefore, a risk figure for the motorcycle must be derived. In the figures published by the Metropolitan Life Insurance Company there were 2½ times the fatalities in 1956, per 100,000 registered motorcycles, as there were in a similar number of registered motor vehicles. In addition, the National Safety Council estimates the accidental death rate for motorcycle drivers to be between 20 and 40 per 100,000,000 vehicle miles as compared with 5.6 for drivers, passengers and pedestrians in all other motor vehicle accidents.

When these facts are analyzed it becomes apparent that careful and deliberate thought is needed on this matter.

In the past, authors from around the world have compiled statistics which reveal that the young male is most often involved. Figures for the motorcycle accident death rate, by age, in the United States for the year 1965 revealed that approximately 60% of those killed were between the ages of 15 and 24[1,2,3,5,6] (Figure II). This is in contrast to other motor vehicle accidents in which the death rate is highest in the teens and falls gradually over the next sixty years.

Gustilo[5] of Minneapolis conducted a study which revealed the following findings: When seventy motorcycle accident victims were surveyed it was revealed that males were involved four times as often as females. Twenty percent were first or second time riders, and seventy percent did not own the cycle on which they were riding. Bauer[1] found in his series that riders with less than six months of experience had about twice as many accidents as those with more.

From the Division of Surgery

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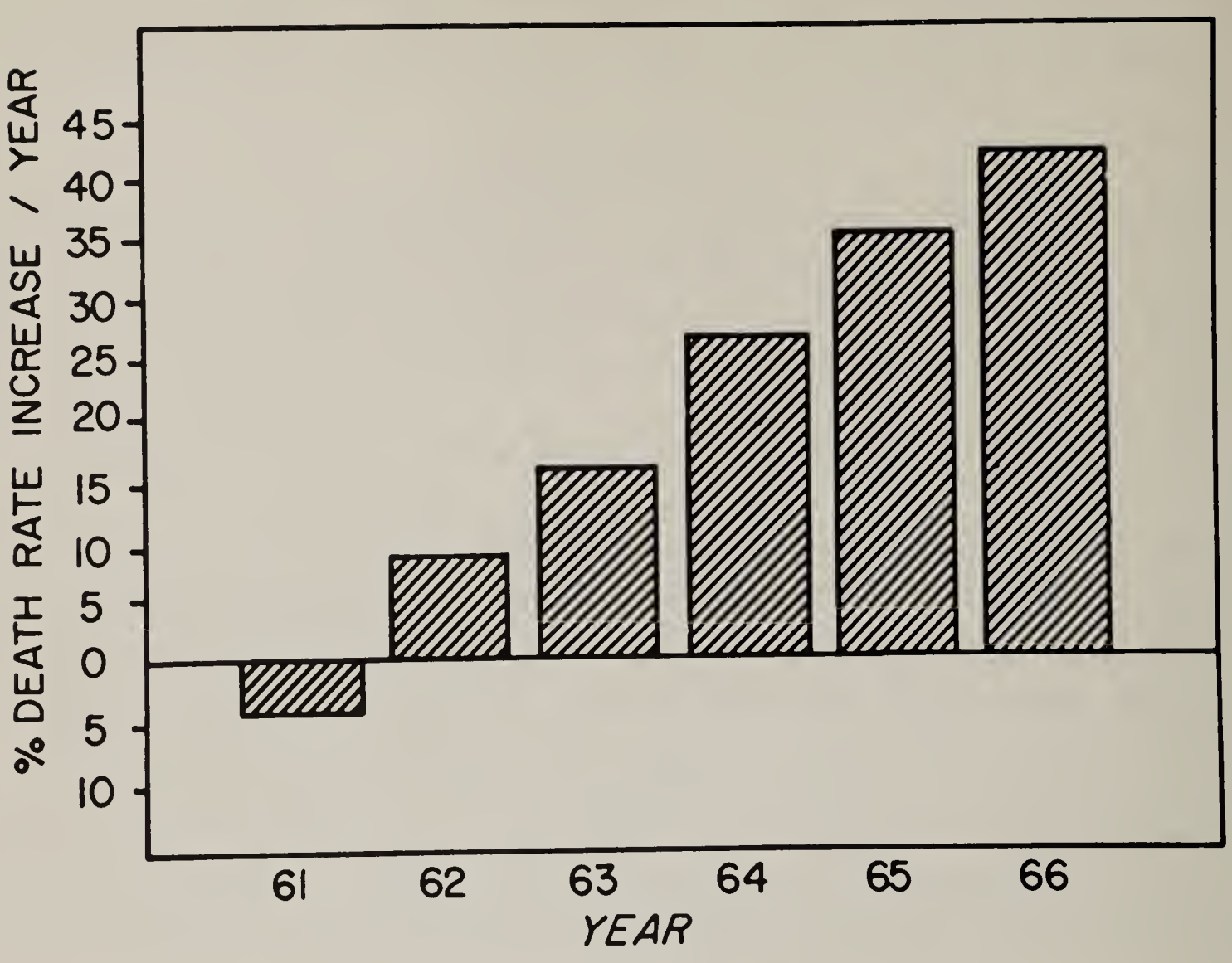

Fig. I

After this six month period, however, the degree of experience made little difference in the accident rate. In addition to the above facts, the nature of the accident was worked out by Gustilo[5]. Thirty-eight point four percent of the accidents were collisions between a car and a motorcycle. The remaining 61.6 percent were accidents resulting from upsets of the cycle by various causes.

To bring the problem into sharp focus it is necessary to review the local statistics for the city of Chicago, as compiled by the Statistical Division of the Chicago Police Department. Their figures indicate that the motorcycle registration in the city of Chicago has risen by 68% since 1962 with a corresponding rise in the accident rate of 66% (Figure III). Further breakdown of the figures indicates that although the accident to registration ratio is rather constant there is a gradual trend upwards in total number of injuries when compared to the total number of accidents (Figure IV).

To this point we have been concerned primarily with the statistics related to the incidence of motorcycle registration, accident and injury. The overall situation will be complete when the medical implications are considered. Bauer[1] in 1957 reported 686 of motorcycle accidents in which he tabulated the incidence of bodily injury as related to the specific areas and the percent fatality when these areas were affected (Table I). These data reveal that the high risk areas are the head and extremities. The head is involved in 49.6% of the cases with a fatality rate of 79.2% when this area was involved. The upper and lower extremities were the next most often involved body segments, 12.5% and 26.8% respectively.

MOTORCYCLE ACCIDENT DEATHS BY AGE, UNITED STATES, 1965

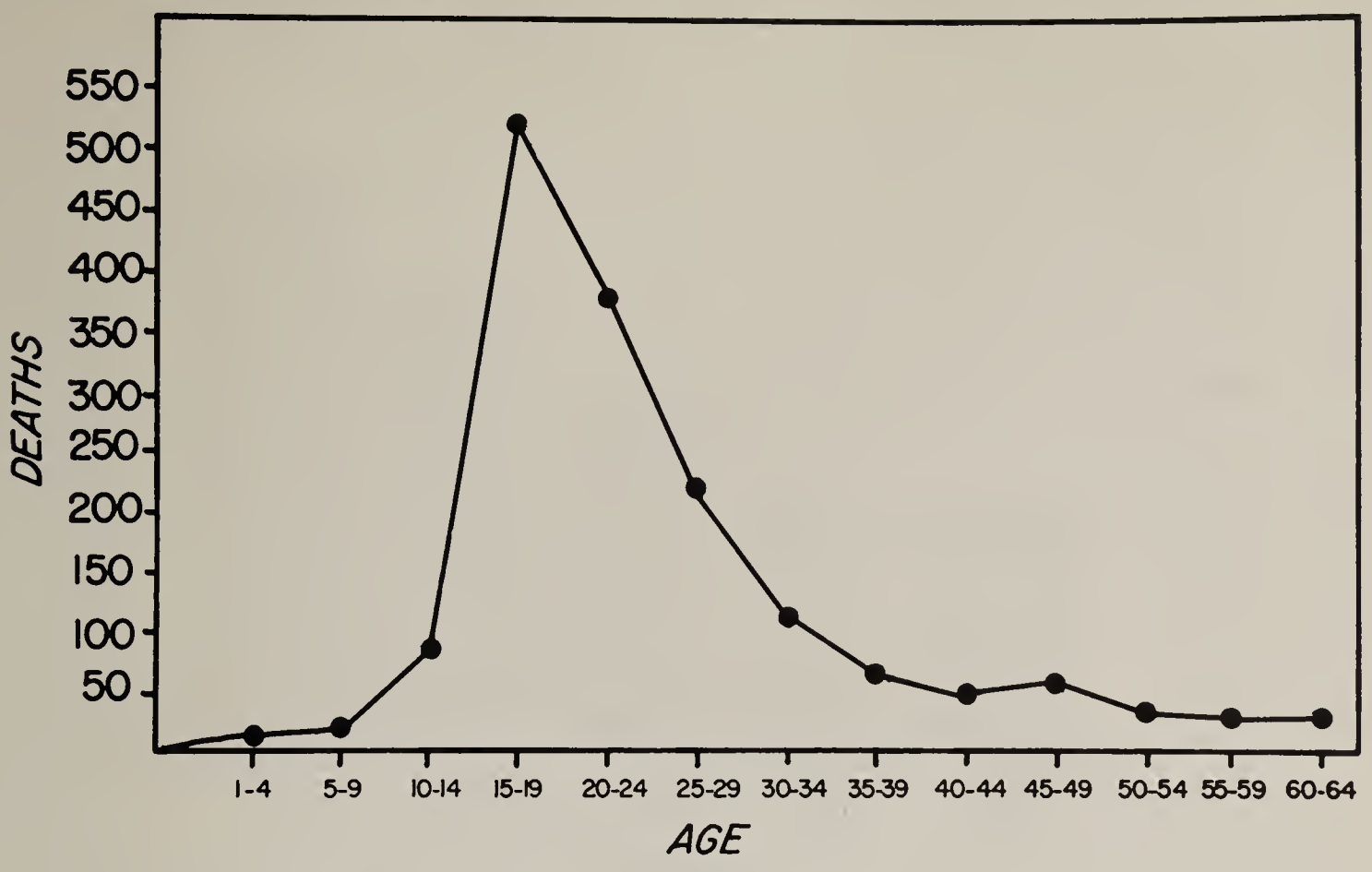

Fig. II

MOTORCYCLE REGISTRATION AND ACCIDENTS IN CHICAGO, ILL.

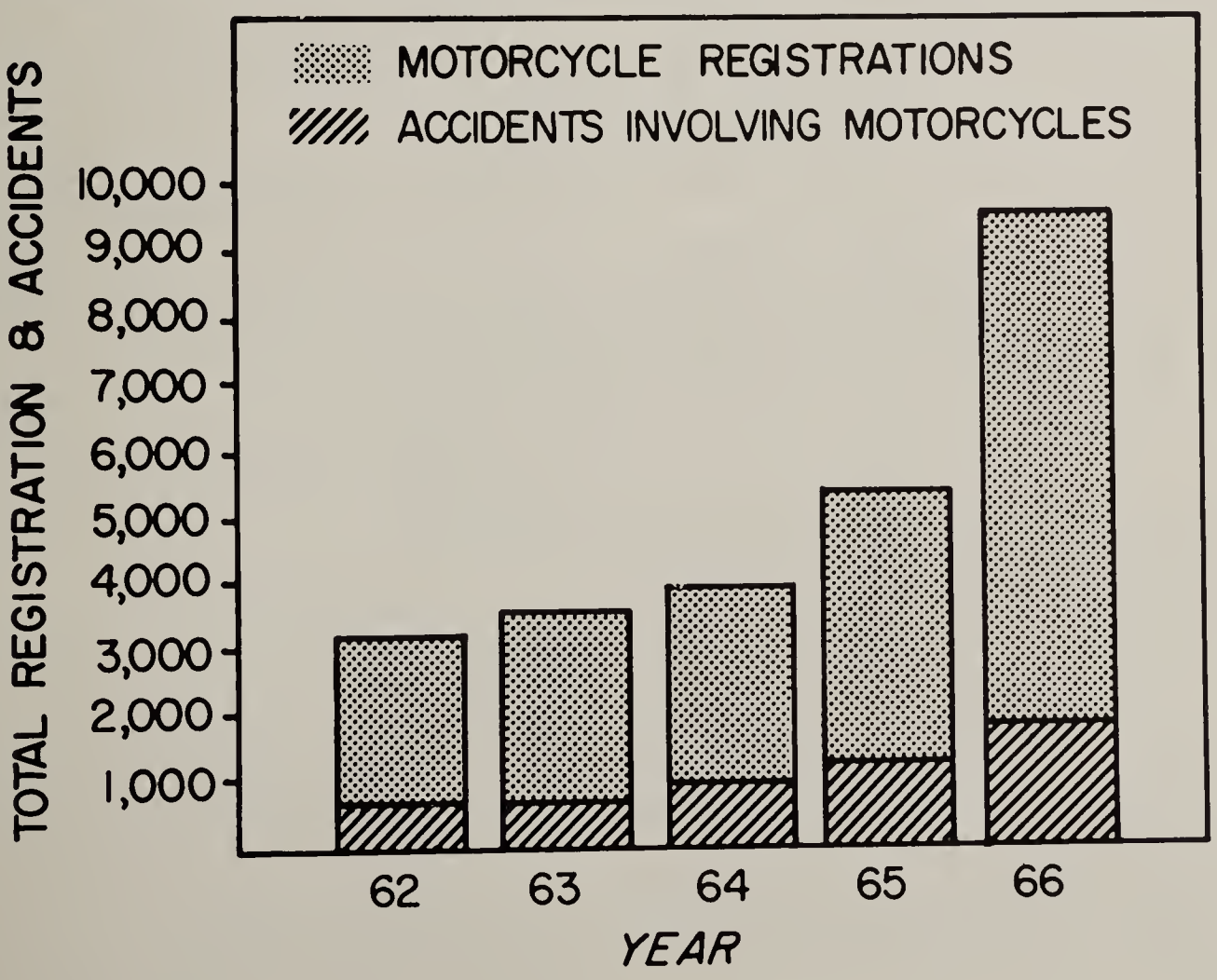

Fig. III

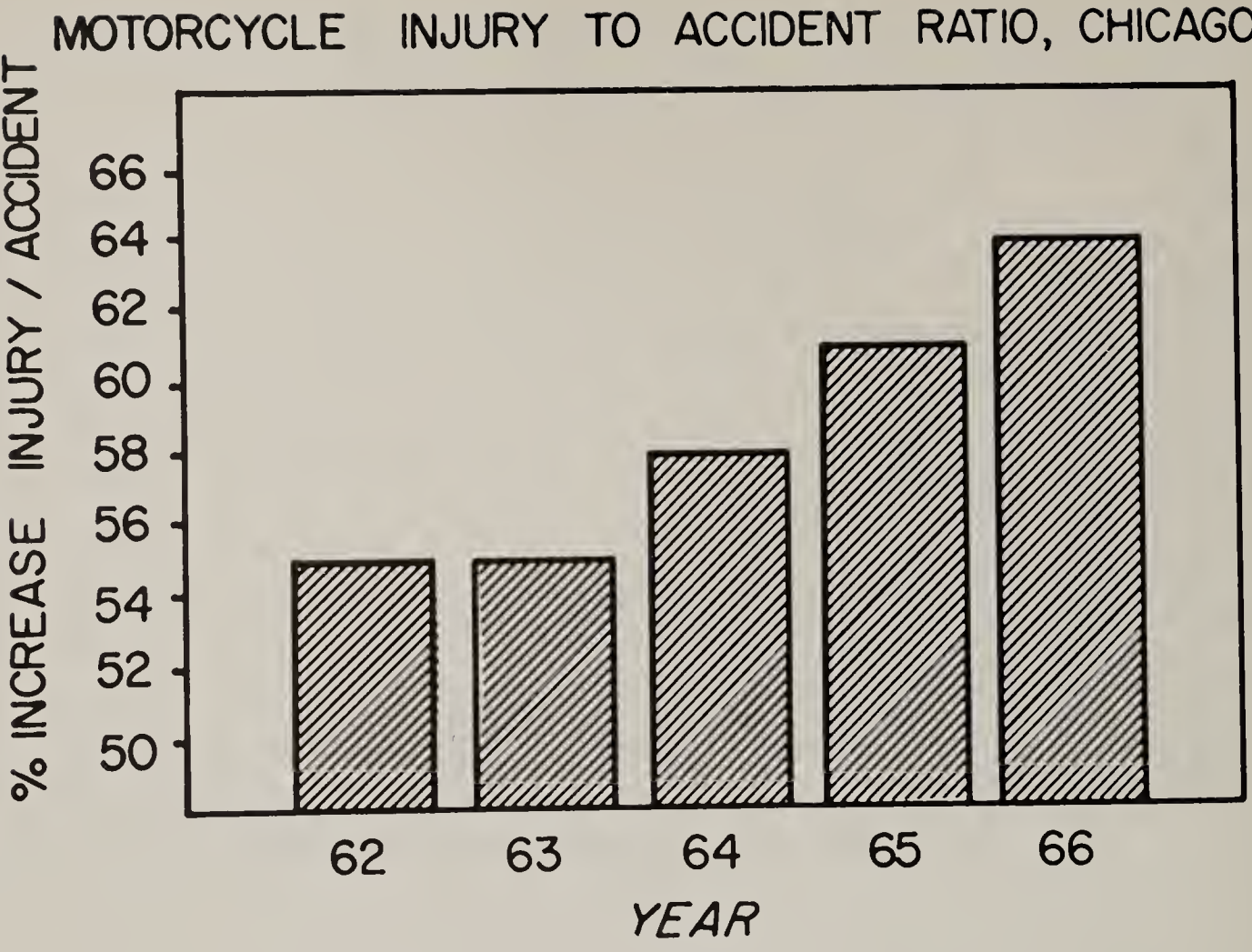

Fig. IV

Bauer, after defining the body segments most often involved, went further and described the typical injury sustained by the head and extremities. These injuries were then broken down as to the mechanism of their injury (Table II).

The following motorcycle accident cases are to further illustrate the type of morbidity and mortality seen in the city of Chicago during the past 1½ years.

Case I

A 17-year-old white male was involved in an auto-cycle collision. Initial examination revealed the following: 1) decerebrate rigidity, 2) numerous fractured ribs, 3) fractures of the humerus, femur, radius and ulna. Sequelae of the accident were recorded as brain damage with diabetes insipidus, gas gangrene of the fractured forearm necessitating below elbow amputation and a below the knee amputation for irrepairable damage of the foot.

Case II

A 23-year-old white female was the passenger on a fatal skidding motorcycle accident. The only protective gear was the patient's helmet, which was hung carefully on the handlebars of the cycle. The patient was admitted conscious with a head laceration and a depressed skull fracture. Surgery was required to elevate the fragment of bone and remove in-driven strands of hair. The patient's recovery was uneventful after the healing of multiple contusions, abrasions and lacerations.

Current Legislation

In the state of Illinois at this time, as in many other areas, there are no special requirements for the driver of the two-wheeled vehicle. The only requirement is that the individual be 16 years of age and have passed a written and practical examination for acquiring a license for the four-wheeled vehicle.

Illinois has, however, recognized its

TABLE I: MORBIDITY AND MORTALITY AS RELATED TO BODY SEGMENTS
(686 CASES)

	Morbidity %	Mortality %
Head	49.6	79.2
Neck	1.8	0.99
Thorax	5.99	7.9
Abdomen	1.7	3.9
Pelvis	1.5	2.9
Upper extremities	12.5	0.99
Lower extremities	26.8	3.96

Ref: Ciba Symposium

TABLE II: TYPICAL INJURIES TO MOTOR-CYCLISTS

Cause	Mechanism	Type of Injury
Fall	a) Body flung through air, head first; skull strikes object b) Fall onto outstretched hand	a) Facial, facial-bone injuries, skull (vault and base) fractures b) Compression fracture of radius
Shoulder hurled e.g. against tree-trunk	Direct impact	Clavicular fractures, dislocation of acromio-clavicular joint, upper-arm fractures, etc.
Arm strikes object	Multiple flexion and/or rotation mechanics	Unilateral double and multiple fractures of upper extremities.
Driver pressed against steering-column	Compression of hand	Fractures of middle hand, wrist injuries; radial fractures in some cases.
Leg strikes object	Multiple flexion and/or rotation mechanisms	Unilateral double and multiple fractures of femur and tibia.
Knee strikes object laterally	Direct compression	Comminuted fracture of exterior femoral or tibial condyle.
Knee strikes object from the front	a) Splintering of patella b) En-bloc displacement of lower third of femur and upper third of tibia c) Longitudinal compression of femur	a) Stellate fracture of patella b) Simultaneous supracondylar femoral and infracondylar tibial fracture (cf. Figure 10) c) Fracture dislocation of hip (cf. Figure 9)
Foot strikes object	Extremity of foot bent violently downwards	Complicated fracture dislocation in Chopart's (medio-tarsal) or Lisfranc's (tarso-metatarsal) joint.

Ref: Ciba Symposium

problems and has taken legislative steps to improve on the afore-mentioned figures. In January of 1969 it will be illegal to drive a motorcycle without first obtaining a license specifically for the motorcycle. This license will be obtained by passing a written as well as a road test on the motorcycle. In addition, drivers under 18 may only operate the low-powered motorcycle. These drivers will also have to present proof of successfully completing an approved driver education course.

In January of 1968 drivers and passengers will be required to wear protective helmets with goggles, glasses or face shields. Effective at the same time is a law stating that the cycle may not carry passengers unless the cycle is equipped with permanent footrests and handgrips. In addition to these specific requirements the cycle must have a rear-view mirror as well as handlebars which do not exceed 15 inches in height.

With these statistics, which are both local and national, it is without doubt that there is a hazard involved in either operating or riding as a passenger the two-wheeled vehicle. The state of Illinois is taking legislative steps to reduce this hazard to the cyclist. Only time and a fresh compilation of statistics will indicate whether or not these legislative steps will improve on the previous five year's figures.

CONCLUSION

To the disbeliever who feels the two-wheeled vehicle is safe, fun to ride, cheap and convenient, the proper advice is, as so aptly stated by Dr. J. C. Drye, a member of the American College of Surgeons Trauma Committee, "Get your son a motorbike for his 'last birthday'."

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TRAUMA TO THE UROGENITAL SYSTEM

Charles T. McKiel, Jr., M.D.[1]

INTRODUCTION

Accidents are the leading cause of death between one and thirty-eight years. With the use of high speed vehicles, multiple injuries involving more than one system of organs or structures are the rule. In a review of a large series of renal injuries, 81% of the patients had multiple injuries of which 61% had associated skeletal injuries and 28% had visceral injuries, including spleen and liver.

This paper will concentrate on injuries to the urethra, the bladder, and the kidneys.

Urethral Injuries

Some common causes of pelvic fractures which can result in injuries to the urogenital system are crush injuries from auto accidents or falling objects, such as barrels or heavy bales and straddle injuries from falling off ladders, fences, bicycles or into manholes.

When considering urethral injuries, the urogenital diaphragm is the most important anatomical structure. It is composed of two layers of dense fibrous tissue separated by one centimeter, and is firmly fixed to the bony pelvis along each descending ramus from the symphysis to a point immediately proximal to the ischial tuberosities. (Fig. 1) The urogenital diaphragm separates the deep pelvic structures from the superficial perineal and scrotal structures, while the male urethra penetrates it near the center making the urethra particularly vulnerable to injury.

Shearing fractures of the pelvis can tear the membranous or prostatic urethra because of its fixed position in the urogenital diaphragm allowing extravasation of blood and urine. When the injury is above the diaphragm, the upward course and the progress of the extravasation is determined by the fascial cleavage planes along the bladder and the prostate.

Figure 2 illustrates the spaces above the urogenital diaphragm where extravasated blood or urine may collect. With a delay in diagnosis or treatment, these products may travel along the ureter up to the kidney (Fig. 3) or may reach the thigh regions and the scrotum through the inguinal canal and spermatic cords.

Ruptures of the urethra below the urogenital diaphragm are limited by Colles' fascia, (Fig. 4) which is distinct from Buck's fascia or the deep fascia of the penis. Buck's fascia being strong, thick and white covers the penile corpora as a strong tube-like envelope and adheres to the underlying tunica albuginea which covers the cavernous spaces. When urine escapes from a ruptured urethra causing a periurethral infection or abscess, it is first contained beneath Buck's fascia resulting in a localized swelling

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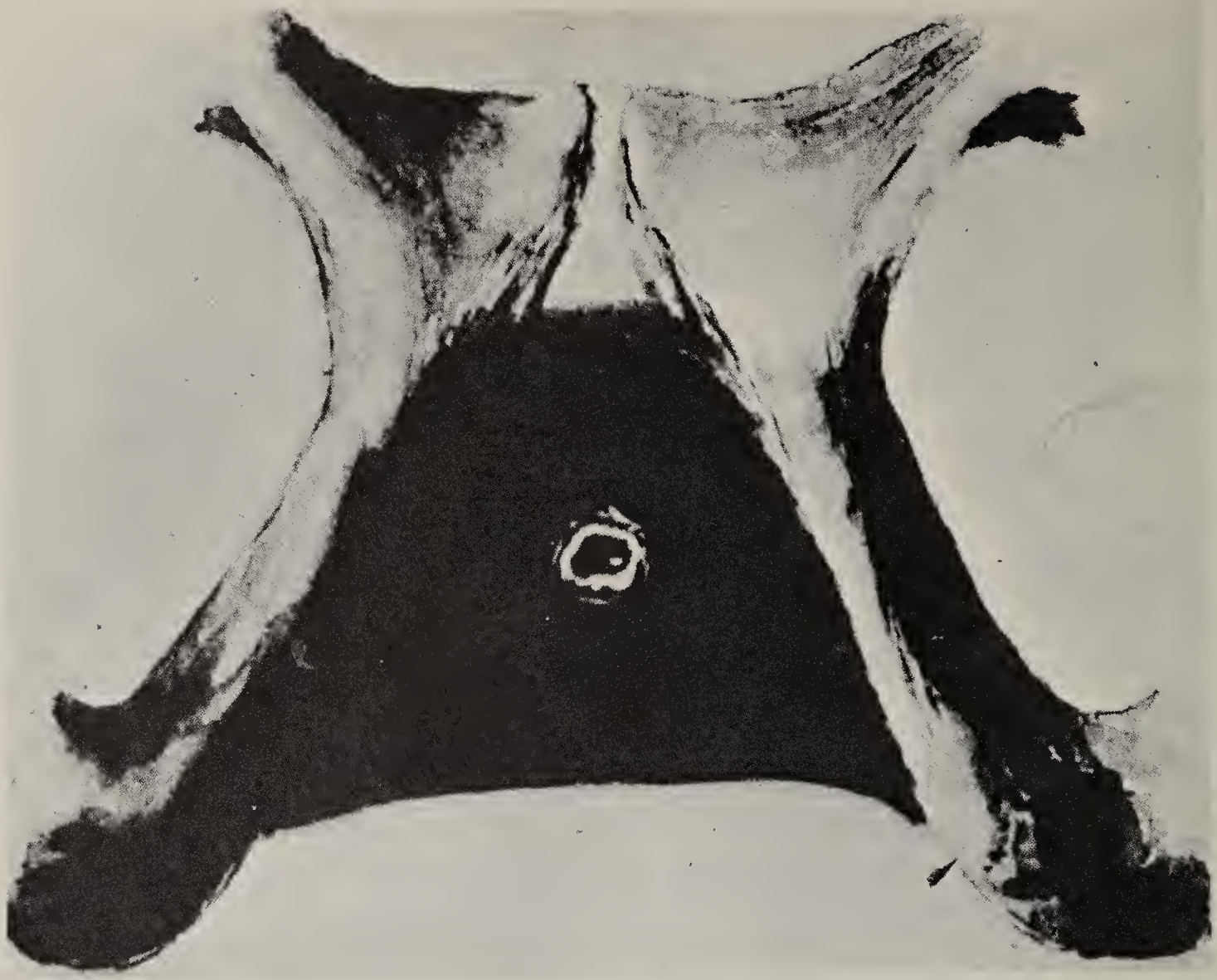

Fig. 1.—Urogenital diaphragm

along the ventral surface of the penis or deep in the perineum.

With penetration of the transverse septum of Buck's fascia, the entire penis may be involved and, should the process rupture through this fascia to collect beneath Colles' fascia in the perineum, the scrotum becomes edematous and in some cases gangrene of the scrotum is seen. (Fig. 5) This collection of extravasates is restricted at the posterior inferior margin of the urogenital diaphragm where Colles' fascia is firmly attached, but it can undermine along Poupart's ligament extending to the abdomen or along the spermatic canal. (Fig. 6)

When minor degrees of urethral rupture are seen early, the patient may show slight swelling with slight but constant urethral bleeding with or without excruciating perineal pain. The same patient several hours later may have urinary retention caused by local edema and periurethral hematoma. The perineum may be ecchymotic with a semifluctuant mass accompanied with local pain increased by pressure from the hematoma.

Treatment depends upon the amount of urethral bleeding and the extent of perineal swelling. If the urethral bleeding is not severe, an indwelling catheter can be inserted. Extensive perineal swelling is an indication for external urethrotomy to divert the urine and evacuate the perineum.

Immediate surgery is necessary if there is interference with urination, marked perineal hematoma, or an impassable urethra. The use of metal sounds, glass catheters, and other fixed instruments in evaluating a possible ruptured urethra should be condemned and a soft rubber catheter be used to determine whether the urethra is passable. Prompt surgery can minimize devitalized urethral and periurethral tissues. Lesions distal to the

Fig. 2.—Posterior urethral rupture with planes of extravasation

urogenital diaphragm should be approached through the perineum. An external urethrotomy is done; the hematoma and extravasated products evacuated and a catheter placed.

In severe urethral lacerations, difficulty may be encountered in recognizing the proximal urethral opening. Adequate perineal exposure to control bleeding, having an assistant press over the suprapubic bladder region to express urine or rectal expression of the prostatic secretion may furnish a clue to the torn urethral opening. If the search fails, it is much safer to perform a cystotomy and retrograde sounding rather than to probe and stab blindly.

After the perineal catheter has been placed into the bladder, the wound may be closed suprapubically, but a suprapubic bladder drainage tube may be utilized. Usually, it is not technically

feasible to suture the urethral ends due to the nature of the injuries, but where possible, primary anastomosis often reduces postoperative stricture. Careful and regular sounding in the post-operative period will result in complete epithelialization.

When seen late, anterior urethral injuries may present massive swelling of the abdominal wall and gangrene of the scrotum. Incision and adequate drainage is necessary. (Fig. 7) The external urethrotomy tube is removed five to ten days postoperatively. The patient usually voids through both the perineal wound and penis after which the urethrotomy wound closes.

Regular urethral sounding after injury is imperative to prevent stricture with resultant irreversible damage to the upper urinary tract. Occasionally, the degree and extent of scrotal and perineal extravasation is so massive that cystotomy with incisional drainage is better than the approved procedures of external urethrotomy and incisional drainage. If cystotomy is performed, the urethra must be repaired within ten days to three weeks or extensive fibrosis will result.

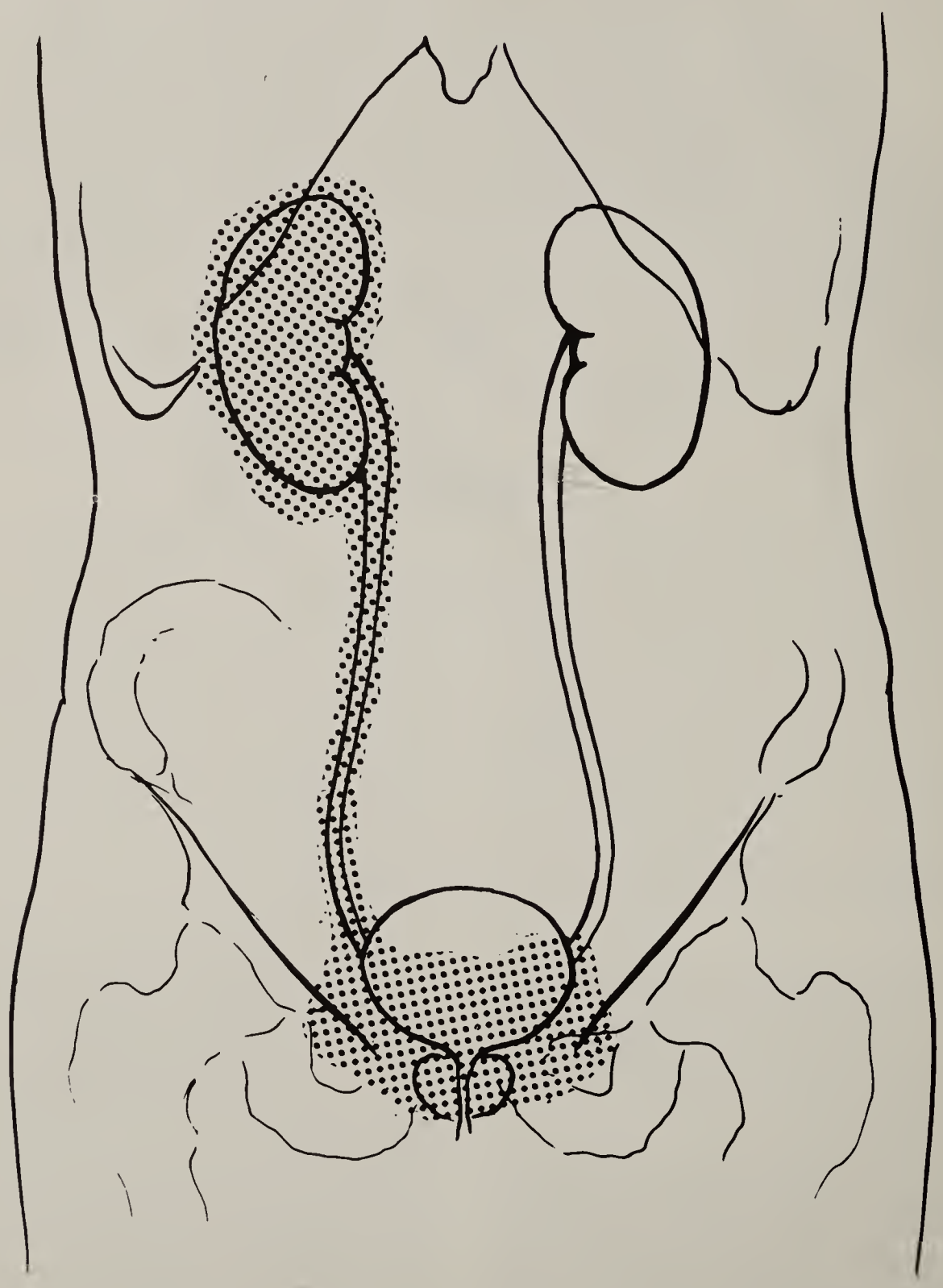

Fig. 3.—Posterior urethral rupture with extension of planes of extravasation to kidney

Ruptures of the posterior urethra are often due to severe auto collisions or industrial accidents which are accompanied by complications of shock, liver and spleen rupture as well as fractures. This urethral injury usually occurs where the urethra penetrates the posterior layer of the triangular ligament or urogenital diaphragm. These injuries range from a simple contusion to a complete separation or avulsion of the bladder neck from the membranous urethra.

Contusion of the posterior urethra may result in urinary retention because of local edema. A catheter may be passed without much difficulty and should be left in place for three or four days until edema subsides. Paradoxically, there may be no apparent interference with urination and yet a rupture of the posterior urethra may be present causing a slow but progressive deep urinary extravasation. Cystotomy with drainage of the perivesical space and splinting of the entire urethra with an indwelling catheter is indicated.

Any patient with urethral damage should be catheterized at once, but if

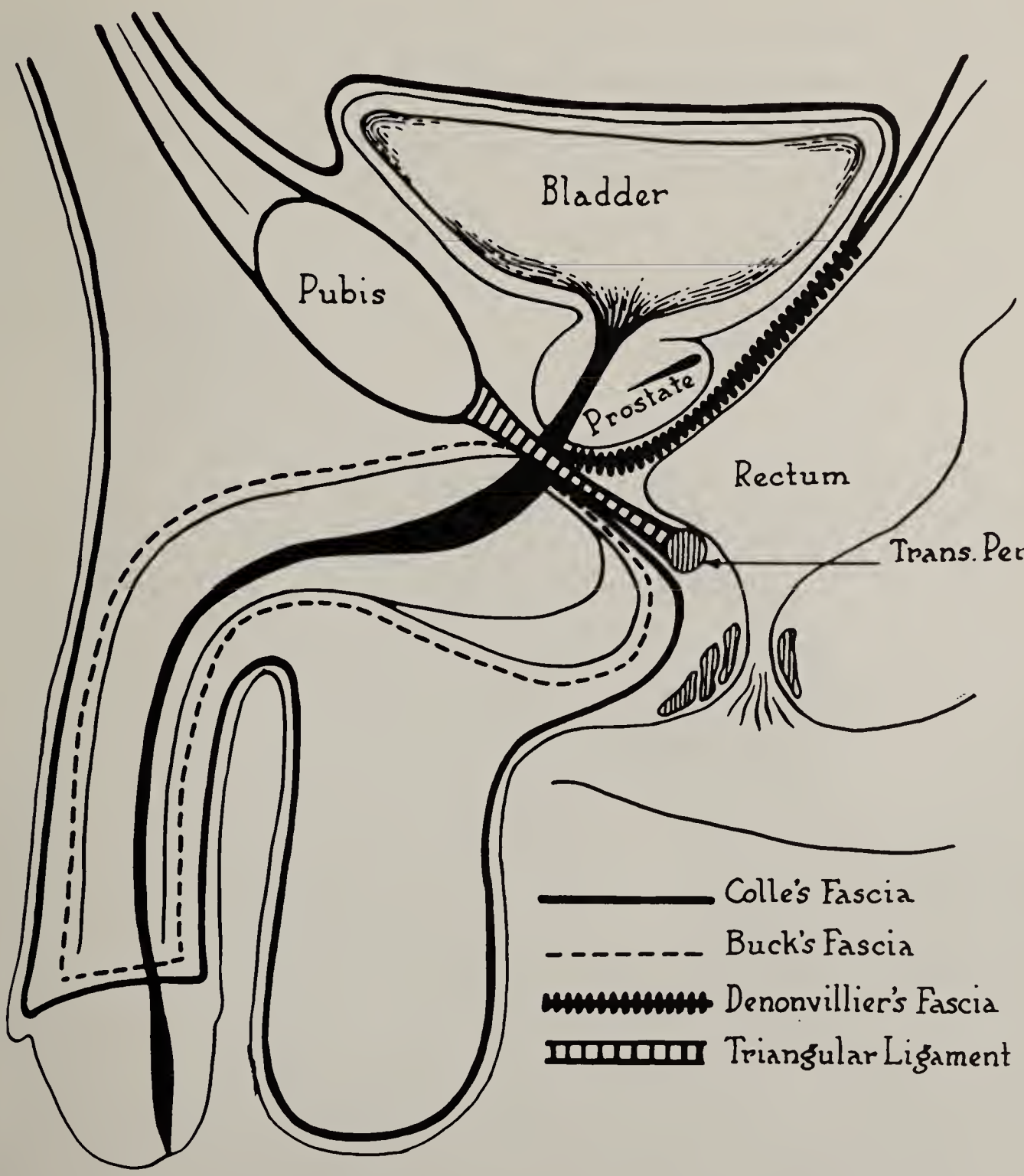

Fig. 4.—Fascial anatomy of the perineum and genitalia

obstruction at the urogenital diaphragm is met, no further instrumentation should be tried. Since the urethral injury and secondary results of the injury are posterior or proximal to the urogenital diaphragm, all surgical approaches should be by the suprapubic route. This approach, and this one only, can drain the perivesical spaces properly, drain the bladder and permit bladder inspection for damaging or free spicules of bone.

After the bladder is opened, a metal urethral sound is passed retrograde through the prostatic urethra and a similar sound is passed through the penile urethra to the urogenital diaphragm. These Davis interlocking sounds are manipulated by the surgeon and then withdrawn into the bladder leading the urethral sound into the bladder. A rubber urethral catheter is attached to the tip of the sound in the bladder and withdrawn through the urethra. A Foley catheter is sutured to this and the red rubber catheter is then brought back into the bladder, the Foley balloon inflated and left indwelling as a splint for the urethra.

The sound which was passed through the entire urethra, besides being the means of placing the catheter, has produced a normal relationship of the two layers of the triangular ligaments and their foramina. It is imperative to place a drain along each side of the bladder down to the prostatic region. The space of Retzius is always drained and the bladder is closed around the cystotomy tube. The urethral catheter is left indwelling for fourteen days.

The temptation to use the perineal approach with an end-to-end suture repair of the rupture of the posterior urethra should be resisted because firstly, the ruptured urethra may not be reached by the perineal route and secondly, the exaggerated lithotomy position necessary for this approach may increase bone displacements with increasing urethral damage. Perineal incision is only indicated when a perineal hematoma is present.

Usually, sexual impotency and sterility result from a posterior urethral injury,

Fig. 5.—Anterior rupture of the urethra with urinary extravasation

but the author has had three men with this injury who have had normal sexual experience and produced children.

In women, superficial urinary extravasation is not seen, but contusion and tears of the female urethra distal to the bladder neck are best treated by an indwelling catheter. Occasionally, the bladder neck is torn off proximal to the urethra and requires cystotomy drainage of both sides of the bladder as well as an indwelling catheter as a guide for re-epithelialization.

Bladder Injuries

Trauma to the bladder occurs in 20% of fractures of the pelvis, even though urethral injuries are more common. The severity of the bladder injury is not related to the extent of the pelvic fracture. The history of whether the bladder was full at the time of the injury is important because a collapsed, empty bladder is almost immune to injury, while a distended bladder can be severely torn from minimal trauma.

Ruptures of the bladder are either

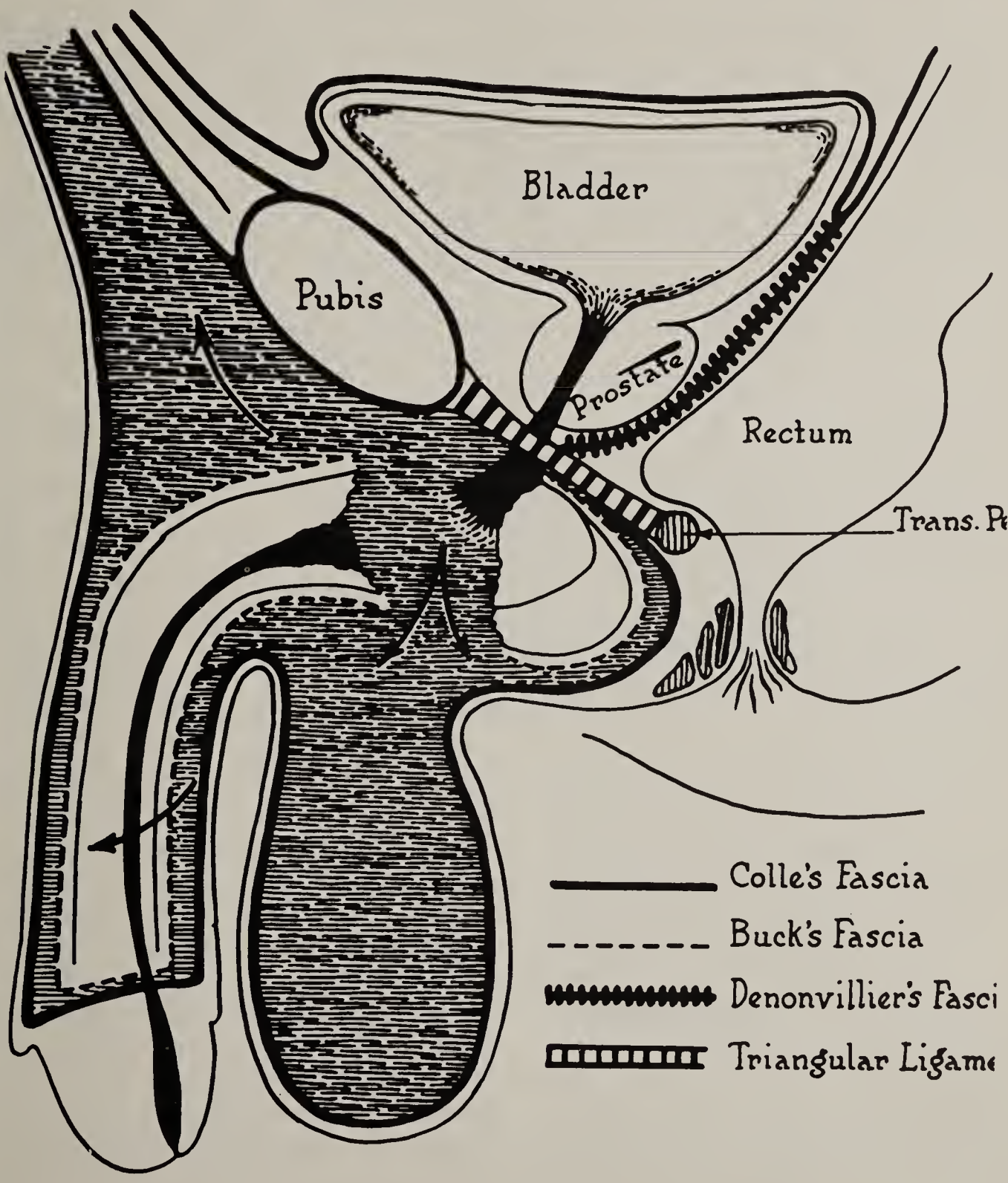

Fig. 6.—Fascial anatomy of the perineum and genitalia in anterior rupture of the urethra

Fig. 7.—Gangrene of the scrotum and anterior abdominal wall secondary to urinary extravasation

extraperitoneal or intraperitoneal. The most common site of the extraperitoneal rupture is the anterior bladder wall and the character of the break is usually linear in the direction of the bladder neck. Intraperitoneal ruptures are found in the dome and posterior walls of the bladder. Most bladder ruptures associated with pelvic fractures are extraperitoneal.

The diagnosis of rupture of the bladder may be easy or very difficult depending on the signs present. Inability to urinate following an accident associated with a pelvic fracture is presumptive evidence of a bladder rupture. The presence of shock, multiple injuries, and neurological lesions accentuate the difficulty of diagnosis. The patient may void clear, blood-tinged, or grossly bloody urine.

Many aids are available to assist in the diagnosis of bladder rupture. Cystoscopy will give direct evidence of rupture showing a true laceration or protrusion of pelvic bone or small bowel into the bladder. However, the lithotomy position necessary for this examination is ill advised in severe pelvic fractures.

A cystogram is the most valuable aid in diagnosis of a ruptured bladder. It is imperative, especially in intraperitoneal ruptures of the bladder, that on cystogram the bladder be fully distended so that a small rent or rupture sealed off by bowel or omentum is demonstrated. The most important film for the diagnosis of extraperitoneal rupture is the postevacuation film in which contrast material will be seen extravasated behind or to the side of the bladder. This may not be apparent on a cystogram in which the bladder is completely full and the extravasated contents are hidden behind the dense full bladder.

Treatment of a ruptured bladder is to divert the urinary current by suprapubic cystostomy, drain the spaces where extravasation has occurred, and establish hemostasis. Frequently, fascial planes are not discrete due to the nature of the injury. In intraperitoneal rupture, the rent in the bladder and peritoneum must

Fig. 8.—Sequestrum of bone removed from bladder

be found and closed, whereas in extraperitoneal rupture, there is no need to find the rent because the bladder mucosa will heal without suture if the urine is diverted. It must be stressed that whether the rupture of the bladder is extraperitoneal or intraperitoneal, the peritoneal cavity must be opened and inspected for blood or fecal contamination because of the high incidence of associated visceral injuries.

Spicules of bone may perforate the bladder wall and a loose fragment of bone within the bladder can be the source of recurrent cystitis following a pelvic fracture. (Fig. 8)

Renal Injuries

Renal trauma is relatively common in multiple injury cases and may be associated with pelvic fractures, fractures of the lower thorax, and penetrating wounds of the abdomen. Hematuria is the most important sign being present in about 97% of renal injuries, of which 70% is gross hematuria. If bladder rupture is

Fig. 9.—Hypernephroma ruptured by blunt trauma

suspected, this must be eliminated by the procedures suggested in the foregoing section.

Renal trauma is divided into blunt or penetrating injury which is comprised of simple or high velocity.

Most renal trauma can be treated conservatively except for high velocity injuries which require surgery. Progressive improvement of the patient warrents continuation of a conservative approach, but progressive deterioration indicates surgical treatment.

Two examinations provide considerable information on renal injuries: (1) an infusion drip pyelogram with delayed films and (2) aortography for a study of the renal vascular system.

The infusion pyelogram can be performed immediately upon starting the intravenous solution if shock is present. A solution of hypaque and dextrose is run as rapidly as possible and films are taken upon completion of the infusion. The presence of the opposite kidney as well as the injury to the involved kidney is demonstrated on the films. If nonvisualization occurs, aortography, either translumbar or retrograde femoral, can visualize the vascular supply of the kidney and the celiac plexus. Straightening of the splenic artery is pathognomonic for injury to the spleen or tail of the pancreas.

When surgical exploration of the abdomen is necessary, such as in a high velocity injury or in an abdomen revealing blood from a four quadrant tap, the urologist should be called to evaluate the kidney injury prior to the intestinal tract surgery as well as after this surgery is completed. A progressive expanding hematoma may require surgery on the kidney, whereas a stable hematoma should not be disturbed. If future intervention is necessary in the postoperative

Fig. 10.—Congenital hydronephrosis ruptured by blunt trauma

period, a standard lumbar approach can be utilized. Uncontrolled hemorrhage is the chief indication for surgery of blunt trauma or simple penetrating injuries of the renal area. During the convalescent period, urinary extravasation producing sepsis is another indication for surgery and this requires drainage through Petit's triangle. In the author's experience of kidney injuries, immediate surgery for a deteriorating situation secondary to blunt renal trauma was needed because of previous renal abnormalities. One case involved a hypernephroma which bled on blunt trauma, and two patients had congenital hydronephrosis. (Figs. 9 & 10)

Follow-up observations are imperative on any renal injury to rule out subsequent damage not apparent during the acute state.

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THE MANAGEMENT OF SEVERE BLUNT CHEST TRAUMA

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INTRODUCTION

Mortality from severe blunt chest trauma and its associated injuries is approximately 46%.[1] If this high mortality rate is to be decreased, the emergency room physician and surgeon must be aware of the pathophysiologic alterations caused by this type of injury and appropriately treat these alterations rapidly and early. Any significant delay can result in death.

Physiologic Alterations

Blunt chest trauma can markedly alter the physiologic function of the chest wall and thoracic organs. One of the first changes that occurs is in ventilatory function. It is often decreased significantly, and several factors can cause this alteration; one of the most common being the flail chest. The ribs and sternum are often fractured in many places, resulting in a "free" portion of chest wall. The flail or "free" portion of the chest wall moves inward on inspiration and outward on expiration. As the intrapleural pressure becomes more negative on inspiration, atmospheric pressure pushes the flail segment in. During expiration the intrapleural pressure exceeds atmospheric pressure and the flail segment is pushed outward. The flail segment moves exactly opposite to the remainder of the chest wall, or is said to move paradoxically. Paradox is usually not seen with posterior rib fractures as the usual supine position of the patient stabilizes the posterior chest wall and the latissimus dorsi muscle and scapula act as splints. Paradoxical motion of the chest wall decreases the efficiency of the chest wall bellows and the efficiency of ventilation is decreased. Edema, chest wall hematoma, and painful splinting of chest wall muscles also reduce chest wall motion and effective ventilation. Blood or air may be present in the pleural space altering intrapleural pressure, compressing the lung, and further decreasing effective ventilation.

Airway resistance is increased due to secretions, blood in the tracheobronchial tree, and bronchospasm. The increase in airway resistance results in an increase in respiratory work. A patient with this type of injury can not maintain an increased respiratory work effort for long and soon effective ventilation is further decreased.

Pulmonary and chest wall compliance, as defined by liters of volume change per centimeter of water pressure change, is decreased. This decrease in elasticity or compliance is due to edema, hemorrhage, retained secretions, and pain. This means it requires more airway pressure to produce the same ventilatory volume change. Due to increased airway resistance and significantly altered respiratory mechanics, it is very difficult for the patient to do this, or he soon fails owing to the effort required.

Direct trauma to the lung itself results in parenchymal hemorrhage and loss of functioning lung tissue. This hemorrhage and area of contusion may then stimulate formation of the "traumatic wet lung." Due to the direct injury, edema

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fluid permeates the interstitial tissues of the lung and fills small bronchioles and alveoli. There is an increase in bronchial secretions due to the injury and bronchospasm develops. Capillary injury results in further formation of edema fluid. Larger bronchi become obstructed with secretions and fluid and, due to ineffectual cough and clearing of the airway, the wet lung becomes progressive. Associated hypoxia then results in more transudate formation. It is readily apparent that a "vicious cycle" is begun unless interrupted by the proper therapy.

The described injuries cause a significant decrease in tidal volume or, in effect, increase the dead space. The ineffectual paradoxical motion of the chest wall, pain, compression of the lung by intrapleural air or blood, and obstructing secretions all decrease the amount of air delivered to the alveoli. The normal compensatory action is to increase respiratory rate but minute ventilation is still low due to the significantly decreased tidal volume. The result is an inadequate elimination of carbon dioxide. The resulting increase in arterial pCO^2 soon gives rise to respiratory acidosis and an arterial pCO^2 in the range of 50 to 60 mmHg. is not uncommon.

Hypoxia is also present in the patient with severe blunt chest trauma. Decreased ventilation results in less oxygen being delivered to the alveolus and a low alveolar pO^2 is the result. Less oxygen diffuses across the alveolar capillary membrane. A second significant cause of decreased arterial oxygen saturation is that ventilation-perfusion ratios are markedly altered in the traumatized lung. Patchy atelectasis, compression atelectasis by intrapleural air or blood, and obstructive atelectasis all result in portions of lung parenchyma not being ventilated. Unventilated lung is perfused by pulmonary blood flow resulting in shunting of venous blood into the systemic circulation. This shunting is a "right to left shunt" and results in hypoxia. Peripheral tissues do not receive an adequate amount of oxygen and metabolic acidosis results.

Cardiac injury and hypovolemia can cause a decrease in cardiac output. The brain and other vital organs are perfused inadequately and metabolic acidosis is further accentuated.

Respiratory acidosis added to the metabolic acidosis of hypoxia and low cardiac output starts an acidosis promoting cycle. Cardiac arrest can be the end result.

Evaluation

Many of these patients are semiconscious and unable to communicate well to the physician. Time should not be wasted in trying to obtain a few jumbled words of history.

An immediate awareness of some of the injuries can be obtained by "visual" inspection. If a flail chest is present, the flail segment can easily be noted by its paradoxical motion. This immediately makes the examiner aware that intubation, tracheostomy and respiratory assistance will be needed and they can be obtained quickly. Subcutaneous emphysema can be extensive and cause puffiness of the eyelids, scrotum, and supraclavicular areas. This indicates a traumatic communication between the pleural space and the subcutaneous tissues and usually a sizable air leak from the lung. Preparations can be made then for the insertion of a chest tube. It is also kept in mind that there may be a laceration of a major bronchus. Any evidence of penetrating wounds should be looked for and their location noted, as this may indicate organs injured and direct further therapy. Distended neck veins, even in the supine position, may indicate obstructed venous return caused by cardiac tamponade or tension pneumothorax. Abdominal distension can mean hemorrhage into the free peritoneal space and immediate laporotomy might be life saving. Rapid confirmation of these initial observations by physical examination and selected laboratory procedures can be life saving. Waiting to "see what the X-ray shows" may be too late.

The initial cursory physical examination can be very helpful in the early management. Low blood pressure is an obvious indication of shock and measures to restore volume must be done immediately. A narrowed pulse pressure can be an indication of cardiac tamponade and, again, if other findings corroborate this diagnosis, pericardiocentesis can be life saving. An elevated systolic pressure might be one further indication of inadequate ventilation with resultant hypercarbia and reinforces the need for adequate ventilation. A rapid pulse correlates well with shock and poor ventilation. A very slow pulse may indicate impending death and emergency procedures should be done rapidly i.e., replace blood loss, decompress a tension pneumothorax, immediately improve oxygenation, or perform a pericardiocentesis. The peripheral pulse should be felt for in the neck and in all four extremities. Lack of, or a decrease, may indicate great vessel injury, especially involving the aortic arch and its branches. This simple observation could save valuable time in repairing a great vessel injury.

Examination of the thorax may reveal significant abnormalities. Palpation can reveal subcutaneous emphysema, fractured ribs and sternum, and fractured clavicle. Deviation of the trachea indicates tension pneumothorax or hemothorax. A tympanitic hemithorax represents pneumothorax and rapid insertion of a chest tube is indicated. Significant dullness would most likely mean a hemothorax and preparations for tube thoracostomy can again be done. Decreased or absent breath sounds can be an indication of fluid or air in the pleural space and also possibly bronchial obstruction. The latter would have to be confirmed by other diagnostic measures. Stridor would suggest injury to the larynx or partial obstruction by a foreign body. Immediate tracheostomy might be life saving. Unilateral wheezing would be produced by bronchial obstruction and could be due to a foreign body, injury to the bronchus, or secretions. Early bronchoscopy would become an important factor in management. Decreased heart tones would be more confirmatory evidence of tamponade.

A portable chest X-ray should be taken as soon as possible. It is best to take the film in the upright position as a large hemothorax may be missed with the patient supine. If it is impossible to sit the patient up, then the film has to be taken supine. Electrocardiogram should be taken to obtain a baseline tracing and to note any possible cardiac damage.

The above type of initial evaluation requires only a few minutes time. These findings can guide the examining physician to immediate treatment of a specific abnormality or to obtaining more specific diagnostic aids regarding the abnormality, any of which can be life-saving.

Treatment

A localized chest injury or a small number of fractured ribs often can be controlled by conservative management. This consists of strapping the hemithorax, intercostal nerve block, drainage of the pleural space of fluid or air, and removal of obstructing secretions by naso-tracheal aspiration or bronchoscopy. One must keep well in mind, though, that it is a common error of judgment to underestimate the severity of the injury and the physiologic derangement. When a flail chest is present, a more vigorous approach is usually indicated.

Initially the oral airway must be cleared and oxygen started. This is done in preparation for oral intubation. A central venous catheter is placed for monitoring of fluid replacement and a second intravenous infusion is started to be used for volume replacement. A Foley catheter is inserted to monitor urinary output and evaluate any genito-urinary damage.

The significant alteration in respiratory mechanics must be changed and the best initial method is by oral intubation and mechanical ventilation. The latter can be carried out by the use of a hand bag ventilator with an increased concentration of oxygen. It readily will

become apparent to the individual maintaining ventilation what pressure and volume is required to promote more adequate ventilation. If a pressure controlled respirator is used initially in the emergency room, it must be remembered that the pressure setting will have to be much higher than normal to combat the effects of decreased pulmonary and chest wall compliance and increased airway resistance. As a patient with a flail chest will require more than 48 to 72 hours of mechanical ventilation, tracheostomy over the endotracheal tube is then done. Tracheostomy will decrease the dead space, allow removal of secretions, and further allow long term continuous mechanical ventilation. Following completion of the tracheostomy, the airway is cleared of secretions by the use of saline and a Coudé type catheter which can be directed into both main stem bronchi.

Attention then must be diverted to the status of the pleural space. An obvious tension pneumothorax requires immediate needle decompression followed by tube thoracostomy. Any size pneumothorax will be increased by mechanical ventilation and a chest tube must be placed to water seal drainage to control the pleural space. There is no room for needle thoracentesis in the treatment of pneumothorax associated with severe blunt chest injury. Rarely, a pneumothorax will not be present and then the surgeon must be aware constantly of its possible development.

The presence of a hemothorax associated with blunt chest trauma requires the placement of a large chest tube. A #32 tube is preferable and size #18 tubes are to be condemned. A large tube is necessary to decompress the pleural space and to monitor blood loss. The tube is best placed in the lower thorax in the posterior axillary line. Air and fluid both will be removed by the tube in this position. Indications for thoracotomy to control bleeding[2] would be (1) continued loss of 300 cc of blood per hour, (2) a remaining large clotted hemothorax after tube placement, or (3) over 1000 cc of blood obtained at the time of initial tube placement.

Arterial blood gases should be determined to establish a baseline for treatment and to establish the physiologic status of the patient.

A repeat chest X-ray should be obtained to evaluate any changes after treatment has been instituted. This is well demonstrated in Fig. 1. Following placement of the chest tube in the right pleural space, the lung did not expand, indicating bronchial obstruction. Bronchoscopy was done then clearing the airway of blood and secretions allowing immediate expansion of the lung. If there is any suggestion of foreign body in the airway or blockage by blood and secretions, bronchoscopy can be done through the tracheostomy. It must be done by an experienced endoscopist to avoid any unnecessary delay as ventilation is markedly inadequate with the bronchoscope in place.

A large air leak through the chest tube may indicate a ruptured main stem bronchus. In this instance, decortication suction must be applied carefully or not at all, as a tension pneumothorax can develop when the suction removes a smaller amount of air than the bronchus leak produces. A second chest tube may have to be placed to maintain lung expansion. If bronchial rupture is suspected, bronchoscopy is indicated to find and evaluate the tear. As soon as the patient's condition is stabilized, thoracotomy and repair is done. Most parenchymal air leaks will decrease and stop, but if large and persistent, thoracotomy and repair is indicated.

The proper respirator for long term management is the volume control type. This was initially described by Avery and Mörch[3] in 1956. When compliance is markedly altered, as in a flail chest, and airway obstruction to varying degrees is present, a respirator which delivers a constant volume, regardless of pressure, is needed. Pressure controlled respirators are designed to shut off when a preset airway pressure is reached. "Adequate" airway pressure will vary due to alterations in compliance and

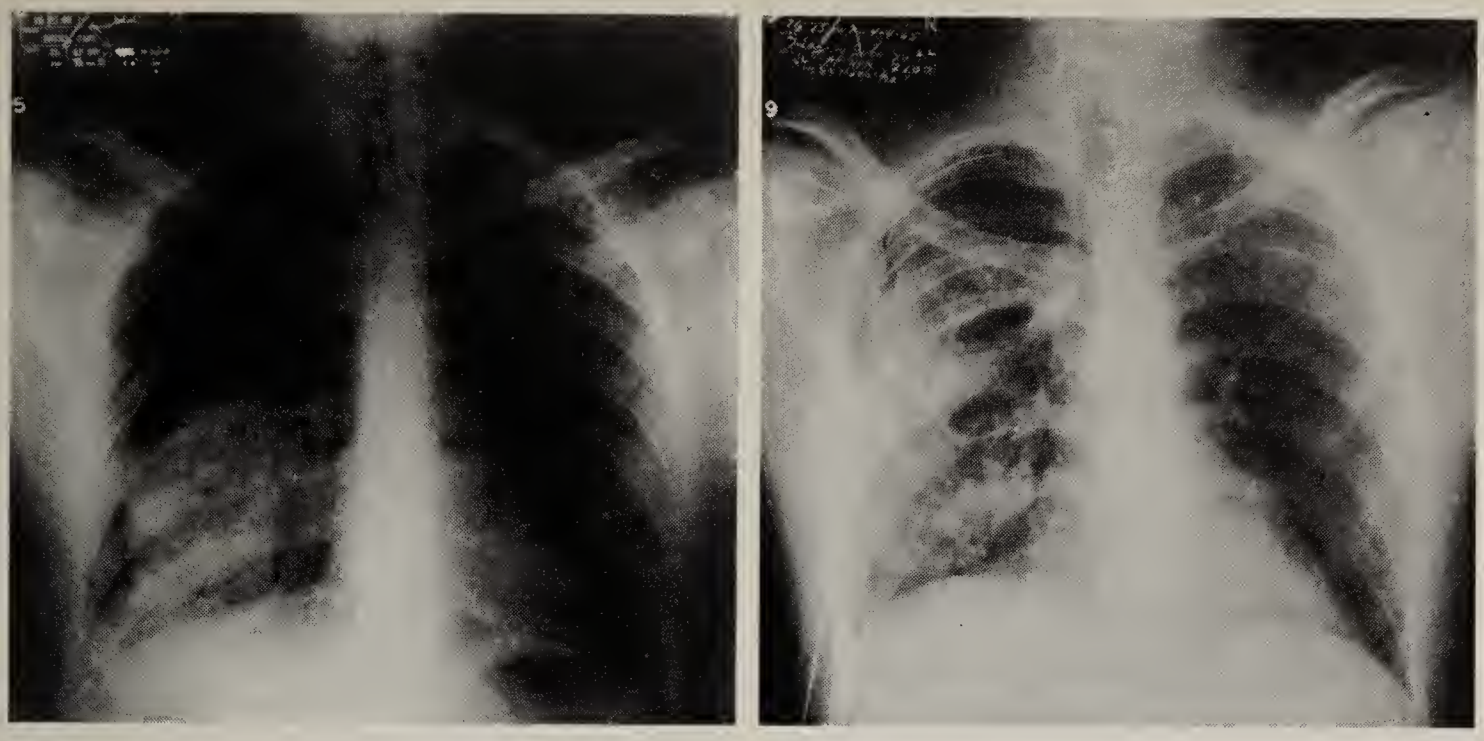

Fig. 1.—Chest x-ray on the left reveals failure of the lung to expand after placement of the chest tube. X-ray on the right shows full lung expansion following bronchoscopy and alleviation of bronchial obstruction.

airway resistance. The pressure setting would have to be varied constantly to satisfy the changing conditions in the patient's airway and lungs. This would require an almost impossible amount of attention by the physician. A volume controlled respirator delivers a pre-determined constant tidal volume. It does this despite changes in compliance and airway resistance. With the constant minute ventilation, airway pressures are allowed to vary and adequate ventilation is maintained.

Assisted respiration is deleterious as the patient is often unable to "trip" the respirator and initiate inspiration. This is due to his pain, paradox, and poor inspiratory effort. If brain damage were present, he also would be unable to initiate inspiration and would not be able to be placed on assisted ventilation.

Initially the patient is hyperventilated, so as to render him apneic. This can be accomplished by hand ventilation with a bag or setting the volume respirator at a rapid rate. With hyperventilation, the $PaCO^2$ drops to 30 mmHg or below and the brain's respiratory center no longer initiates respiratory effort. After the patient becomes apneic, the respirator expands the lungs in a slow, even manner. The flail segment is pushed outward by the lung with the other parts of the chest wall. As the patient is apneic, expiratory effort is entirely passive and intrapleural pressure is not markedly more positive. The flail portion of the chest is not forced outward and contracts evenly with the lung and remaining chest wall. Thus, the paradoxical effect is lost.

Oxygenation is improved by mechanical ventilation. A higher concentration of oxygen is delivered to the alveolus by oxygen supplement. No higher than a 40% concentration of oxygen over a prolonged period is preferable, as oxygen toxicity may damage the lung. Improved ventilation also improves alveolar ventilation and more oxygen is delivered across the capillary membrane. Shunting is decreased by expansion of the lung and also by the aspiration of secretions. All aspects of atelectasis are decreased and ventilation-perfusion ratios are closer to normal.

The above therapeutic measures break the acidosis cycle and the patient is maintained physiologically in a slightly alkalotic state.

It is necessary to monitor the arterial blood gases frequently, especially in the

early mechanical respiratory management period. One does not want to hyperventilate the patient massively as indicated by severe respiratory alkalosis nor does he want to underventilate the patient. If the $PaCO^2$ can not be brought into the low 30's mmHg, causes of failure must be diligently searched for. These would be: inadequate tidal volume, low minute ventilation, significant airway obstruction, excessive leak around the tracheostomy, excessive air loss through the chest tube, and large hemo or pneumothorax.

Occasionally the chest wall may be so badly deformed that external traction may be needed. This can be done by placing towel clips around 4 or 5 ribs and attaching 4 to 6 pounds of weight over 2 pulleys on a frame. It can usually be discontinued in 12 to 14 days.

The respirator has to be used as long as it is necessary to provide adequate ventilation. This is best determined by continued monitoring of blood gases. The patient can usually be weaned from the respirator after 14 days, depending on the severity of the chest wall derangement.

Other Injuries

Damage to other vital organs may occur. The heart is often injured and cardiac contusion, heart valve disruption, and myocardial laceration have to be looked for. The great vessels can be lacerated and false aneurysms are frequent. If great vessel injury is suspected, angiogram must be done as soon as possible, followed by thoracotomy and repair, if indicated. The esophagus, diaphragm, and thoracic duct can all be lacerated. Liver, spleen, and bowel injuries must be searched for and repaired as indicated.

SUMMARY

The management of severe blunt trauma to the chest requires:

1. Rapid assessment and evaluation
2. Adequate ventilation and oxygenation
3. Control of the pleural space
4. Maintenance of bronchial lumen and continuity
5. Awareness and appropriate treatment of other injuries

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PENETRATING AND NON-PENETRATING ABDOMINAL WOUNDS

Robert W. Jamieson, Ph.B., M.S., M.D.[1]

INTRODUCTION

The following is a discussion of the problem of acute abdominal conditions caused by penetrating and nonpenetrating injuries to the abdomen. The author's impressions are based upon his experience with the management of such problems while in the military service and as an attending surgeon at the Presbyterian-St. Luke's Hospital in Chicago since 1954.

Incidence and Etiology

Contributing to the swelling incidence of acute traumatic abdomens are the growing number of automobile accidents and the greater tendency towards violence among our people. Perhaps one good thing which may come out of the hostilities in Viet Nam will be an increased number of physicians oriented towards the efficient management of acute surgical abdomens resulting from injury. Battalian surgeons in Viet Nam are learning as was found during the Korean "Police Action", that about ten percent[10] of the casualties have surgical abdomens. About 90% of these cases are due to penetrating wounds and the rest are of the non-penetrating variety following blast injuries, falls and army vehicular accidents. Contrast the ratio of the penetrating abdominal injury to the non-penetrating or blunt injury in civilian practice where only about 15% of the acute traumatic abdomens result from penetrating wounds. The vast majority result from blunt trauma. About three-fourths of the civilian penetrating abdominal wounds are caused by knife injuries while gun shot wounds run a poor second.

In the author's experience less than 1% of the emergency cases treated in the hospital emergency room fall into the category of the acute traumatic abdomen, half of these being non-penetrating injuries resulting from automobile accidents. The statistics gathered at a particular hospital will reflect, to a certain extent, the location of the hospital. The hospital near the expressway probably will admit more cases of abdominal blunt trauma while a hospital distant from arterial highways may have more penetrating injuries.

Pathology

Whereas penetrating injuries usually cause multiple organ injuries to hollow viscera, the blunt abdominal injuries are more likely to affect single, solid organs. Table I indicates the percent frequency of penetrating injury to various intra-abdominal structures in the author's series of cases. Despite the fact that most of the cases in this series occurred in Korean military conflict, the distribution of organ injuries is quite similar to those encountered in penetrating civil injuries. Table II indicates the relative frequency of injury to various intra-abdominal organs from non-penetrating trauma.

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TABLE I: ORGAN INJURY—PENETRATING TRAUMA RECEIVED IN MILITARY CONFLICT

Small bowel	42%
Liver	21%
Colon	26%
Spleen	14%
Stomach	12%
Kidney	12%

Signs and Symptoms

The injured patient's sensorium may be obtunded by age, alcohol, drugs, hypovolemic shock or an injury to the central nervous system. In such cases, the physician's task is rendered much more difficult and the chances of diagnostic error will be increased.

Another factor influencing the signs and symptoms is the time lapse between injury and the first examination. Following abdominal trauma, there may be an interval in which the patient or victim is relatively comfortable. Then, as hemorrhage or leakage progress with subsequent peritoneal irritation the signs and symptoms of an acute abdomen will appear.

The extent of the intra-abdominal injury governs the signs and symptoms of the patient. The patient with a small laceration of the liver or an injury deep in the pelvis may be slow in developing the cardinal signs of tenderness, muscle rigidity and absent bowel sounds. Usually the most dramatic signs and symptoms are seen in the patients with multiple organ injuries in which there is rapid and gross peritoneal irritation. At times the injured anatomical structure may be retroperitoneal and for this reason peritoneal signs may be minimal despite extensive tissue damage.

Diagnosis

When a patient has a definite history of any extensive abdominal trauma with marked abdominal tenderness, rigidity and absent bowel sounds, the problem is not one of diagnosis but rather one of resuscitation and immediate celiotomy. There is little indication for subjecting such a patient to extensive x-ray studies and other diagnostic procedures. In a less urgent situation routine diagnostic laboratory and clinical tests should be reserved for those cases of suspected intra-abdominal injury where there is a question of the organ involved so as to determine whether surgical exploration is indeed indicated.

Treatment

When such emergencies are first seen the patient's airway assumes first priority and should be checked. If the airway is inadequate immediate steps should be taken to provide ventilation. Tracheotomy sets and equipment for intubation with an endotracheal tube should be standard emergency room equipment. After establishing a good airway and controlling active hemorrhage the patient's clothes are completely removed. Vital signs are recorded and a rapid estimate of the injuries and general condition of the patient is made. Occasionally, the patient's clothing will help the physician to determine the extent of the blood loss as well as the missile course of the penetrating abdominal wound(s).

TABLE II: ORGAN INJURY—NON-PENETRATING TRAUMA[10] RESULTING FROM CIVILIAN ACCIDENTS

Kidneys	42.5%	Retroperitoneal Area (hematoma)	9.6%
Spleen	26%		
Liver	18.1%	Bladder	9.1%
Pancreas	5.1%	Small Bowel	7.9%

A rapid search should be made for telltale ecchymotic areas on the abdominal wall in the case of non-penetrating wounds. Wounds of entrance and exit are sought in the case of penetrating trauma.

A large bore intravenous conduit is established and blood is drawn for type and cross-match. Serum amylase levels may be helpful particularly in cases of upper abdominal trauma. X-ray equipment present in or near the admitting area often is extremely helpful to locate the site of a missile, to check for associated fractures or to look for concomitant intrathoracic pathology in a case urgently requiring abdominal exploration.

It must be constantly kept in mind that non-penetrating abdominal wounds are usually associated with other organ injury. During the period of initial treatment a nasogastric tube is placed in the stomach and an indwelling catheter in the bladder. The naso-gastric tube decompresses the upper gastrointestinal tract, helps localize the pathology and discourages subsequent distension. The indwelling bladder catheter also may help localize or identify the site of the injury. It decompresses the bladder and assists the physician in his estimate of hypovolemia.

If the patient is in a state of hypovolemic shock before typed and cross matched whole blood is available, it may be necessary to substitute plasma, dextran or type 0—RH negative blood in an attempt to maintain life until the specific matching whole blood is available. One should be hesitant about infusing more than 1000 cc of dextran because of the possibility of interfering with the patient's coagulation mechanism. Immediate celiotomy should be performed on patients in hypovolemic shock who do not show improvement after rapid infusion of 1500 cc of whole blood in a period of thirty minutes or less. These people have active large vessel hemorrhage which must be controlled despite the great operative risk.

In these critically ill patients very little narcotics or sedatives should be given for fear of aggravating the shock state.

Fortunately, many patients with surgically acute abdomens resulting from trauma are less urgent. The physician can approach their treatment with more deliberation without appreciably changing their morbidity or mortality by the additional delay required by a more thorough pre-operative investigation. It may be helpful, at times, to have the patient swallow some contrast media or undergo an intravenous pyelogram. The insertion of a polyethelene catheter within the abdominal cavity, or a four quadrant paracentesis[17] helps to establish the presence of hemoperitoneum. Injection of Hypaque into the wound of entrance may establish the diagnosis of a penetrating wound.[6] The physician should remember that in the most experienced hands, the four quadrant tap is only 75% accurate. A negative tap means little if anything.[16]

Occasionally one will encounter a case with a wound of the abdomen but few signs of peritoneal irritation. In such cases the wound should be explored first and as it is being debrided the surgeon should determine whether it extends through the peritoneum. Should he find peritoneal penetration he then must explore the abdomen through an approach incision.

Generally, the incision should be placed vertically rather than transversely so as to allow better exposure. The suspected pathology, the point of injury and the pre-operative site of maximal muscle defense dictate whether the vertical incision should be on the right side or on the left side of the patient. A long midline exploratory incision also affords rapid and wide exposure with little bleeding in some cases.

Before the abdomen is opened the surgeon must be certain that there is an adequate amount of compatible blood available and that the suction apparatus is of large caliber and in working order. After opening the peritoneum there is often a sudden drop in the patient's blood pressure. If this drop is anticipated,

it can be more effectively avoided or checked by accelerating the rate of blood replacement, Trendelenburg position and and vasopressors.

The first objective after entering the peritoneal cavity is to aspirate and remove enough blood, bowel content, bile and urine to be able to see and control points of active hemorrhage. The extent of the damage is then assessed and a corrective surgical plan of action formulated. At the conclusion of the definitive surgical procedure, the abdominal cavity should be generously irrigated with warm normal saline. If drains are employed, they should be brought out through separate stab incisions. It is better to risk a small hernia at the drain site than to make the drain site incision so snug that the drains are rendered ineffectual. Delayed closure of the wound of entrance should be considered. Antibiotics should be started early if there is gross peritoneal contamination.

Specific Intra-abdominal Injuries

Small bowel: The small bowel is the most commonly injured intra-abdominal structure and these injuries are almost invariably due to penetrating trauma.

Among the civilian population, the knife causes most of the penetrating injuries while among soldiers the shell fragment is the most common cause. The surgeon must look for an even number of perforations, always remembering that perforations along the mesenteric border of the bowel are easy to miss.

Hematomas of the mesentery should be left alone unless they are expanding, or there is no pulsation in the vessels distal to them, or if they are near an area of small bowel requiring resection. Larger holes (greater than 1 cm) should be closed with the classical two layer technique while small rents may be closed with a one layer, seromuscular, interrupted technique. It is rarely necessary to drain the abdomen In my experience about 20% of these cases require a small bowel resection. In cases where the distal end of the ileum is damaged beyond repair, it is better to perform a right colectomy and ileotransverse colostomy than to attempt to close the ileocecal junction and implant the ileum on the ascending colon. Exteriorization of the injured ileocecal area should only be done if the patient's general condition precludes a more desirable procedure or if the colon is packed full of hard fecal material.

Kidneys, ureters and bladder: Taking perhaps some liberties with terminology, it could be said that the kidneys are the most commonly injured of the solid, viscera after blunt trauma to the abdomen. If gross or microscopic hematuria were to be used as an absolute indication of renal exploration many needless laparotomies would be done. Certainly only a few of the total number of cases seen with hematuria subsequent to trunk trauma will need exploration. Signs of progressive hemorrhage and/or urine extravasation will indicate to the surgeon which cases fall in this category. At exploration every effort should be made to preserve the fractured kidney. The kidney bed should be generously drained. Pre-operative pyelograms are helpful in determining the extent of the injury and the functional state of the uninjured as well as the injured kidney.

When ureteral disruption is suspected it is usually wise and helpful to introduce ureteral catheters transurethrally prior to the exploration. If facilities are available and time permits, a retrograde pyelogram may be attempted before the abdomen is opened. Damage to ureters from blunt and penetrating trauma to the abdomen is extremely rare. This resistance of the ureters to trauma is no doubt a reflection of their small caliber, great elasticity and protected retroperitoneal position. The presence of ureteral catheters aids the surgeon in identifying the ureters which may be surrounded or displaced from their normal positions by retroperitoneal blood. An intraluminal catheter is a necessity in the repair and post-operative management of damaged ureters. If anastomosis is impossible due to the fact that a long segment of the ureter has been destroyed, cutaneous or

enteric ureteral implantation should be accomplished. The ureteral bed should be adequately drained.

After repairing bladder injuries, in most cases, it is wise to use both suprapubic as well as transurethral catheter drainage post-operatively. If the rent repaired has been small and the likelihood of post-operative clots minimal, transurethral catheter drainage is sufficient.

Urethral injuries almost always follow blunt trauma with fracture of the pelvis. An attempt to insert a bladder catheter transurethrally should be made as soon as possible with contrast media being injected to make certain that the catheter is actually in the bladder. If the catheter is found to be in the bladder, its bag is inflated and a one pound traction force is put on the catheter. In a large number of these cases, a cystotomy will be necessary before proper catheter drainage can be effected.

Liver: Lacerations of the liver are commonly encountered after both blunt and penetrating trauma. It is surprising how often the sites of laceration are not bleeding when the injured liver is inspected during surgical exploration. The surgeon will not have treated many of these lacerations before he will learn to suture all of them and drain the liver area through a separate stab wound to avoid delayed bleeding and bile leakage. If the liver injury is near the liver hilus, and certainly if there is major bile duct involvement, "T" tube drainage should be employed for post-operative ductal decompression and splinting. It is interesting that diagnostic paracentesis was only positive in 18 of 51 proven cases of ruptured liver in a series reported by R. S. Brittain.[2]

It should be remembered that many of the patients with liver injuries complain of right shoulder pain and often have a leukocytosis in excess of 15,000.

Colon: The colon is rarely injured by blunt abdominal trauma while it is frequently perforated by penetrating wounds of the abdomen. If the penetrating injury is caused by a shell fragment or a bullet, the surgeon exploring such an abdomen must search carefully for an even number of holes in the colon wall or find the missile within the lumen. If the time interval between injury and surgery is less than three hours, the colon empty, the fecal spill minimal and the injury located proximal to the hepatic flexure, the rent or rents may be sutured without colostomy and the abdomen generously drained.[9, 11, 12] These drains should not be completely removed before the tenth post-operative day. Most of the cases of traumatic injury to the colon are more safely treated by colostomy at the site of injury or by closure of the point or points of perforation with proximal colostomy. Colostomy closure may be done anytime after two weeks depending on the extent of the injury, the general condition of the patient and the degree of peritonitis associated with the injury. If it is inexpedient to exteriorize the injured segment of colon, a proximal diverting colostomy is performed; drains should be placed down to the area of colon repair and allowed to emerge through a separate stab wound in the abdominal wall. Fewer complications will result if colostomies are brought out through separate incisions rather than through the major exploratory incision. In the case of extensive injuries to the colon in the region of the ileocecal valve, the surgical procedure of choice is a right colectomy and ileotransverse colostomy. In all colon injuries antibiotics should be given for at least five days post-operatively.

Spleen: The patient with a ruptured spleen following a penetrating wound usually does not present much of a diagnostic problem and treatment is obvious. The surgeon managing such cases must, however, be certain that the patient does not also have an accompanying thoracic injury. When blunt trauma is responsible for the ruptured spleen diagnosis may be most difficult. Often the patient will now show the classical signs of blood loss, rising WBC, shoulder pain, muscle spasm and abdominal tenderness. In such cases a diagnostic paracentesis may be helpful and the determining factor in whether

early surgery is done or a late diagnosis made and probably subsequently reported as another "delayed rupture" of the spleen.

Suspect cases should be followed for at least two weeks.[13] It is wise to drain the splenic bed and also to search for other injuries. The main cause of the high mortality rate is the fact that there are frequently associated injuries.[3] A large number of post-splenectomy patients develop subphrenic abscesses and pulmonary infections. For some strange reason the "post-splenectomy fever" of yesteryear is rarely seen today but I am convinced that such an unexplained syndrome does exist.

Pancreas and duodenum: Many patients with injuries affecting the duodenum and pancreas die before they can be transported to the physician. Hemorrhage is an important factor in these cases[4] due to the vascularity of the pancreas and duodenum and the proximity of these structures to the great vessels. When dealing with injuries to the duodenum and pancreas, the physician must be prepared to handle profuse bleeding from the great vessels.[14] Most of these cases result from automobile accidents and the incidence of associated injuries is very high. Nearly half of them also have injuries of the liver and biliary tract.[7] About 70% will show an elevated serum amylase and a like number will show free air if the duodenum is ruptured. The most common site of injury is the second or third portion of the duodenum and the junction of the head and body of the pancreas. When it is the posterior wall of the duodenum that breaks down after impingement on the vertebral column, the symptoms may come on days or even weeks after the injury.[5] The surgeon's approach to the injured pancreas and duodenum will be determined entirely by the magnitude of tissue destruction and the general condition of the patient. Simple tears in duodenum or pancreas may be sutured and the area drained while more extensive injuries require more extensive surgery. If the pancreas has been severly crushed and its main duct transected the surgeon should consider distal pancreatectomy and Roux-en-Y drainage of the proximal stump.[7,1] A gastroenterostomy may help promote healing in cases with extensive injury to the duodenum.[8] If there is a question in the surgeon's mind regarding the capacity of the distal bile duct to carry on its function, "T" tube drainage of the common duct should be instituted.[5] At the time of surgery the lesser omental space should be widely opened to help the surgeon accurately determine the extent of injury. Hematomas in the wall of the duodenum should be evacuated. In the post-operative period the incidence of pancreatitis, fistula formation, pseudocyst formation, wound dehiscence and abscess formation are high. If the amylase rises after the fifth post-operative day the patient may have pancreatitis. In a series of 40 cases with pancreatic injuries, Sturim reported[15] 74 complications and the mortality rate in most series runs around 40%. In cases with severe injury to duodenum and pancreas, some have recommended diverticulization of the duodenum by means of vagotomy, antrectomy and gastrojejunostomy.[7]

SUMMARY

As automobile and non-automobile violence become more popular in our advancing civilization the so-called traumatic abdomen is becoming a greater problem. Early diagnosis and treatment will reduce mortality and morbidity statistics. Although the most important factor in the care of this type of injury must still be repeated clinical evaluations by an experienced physician, aid in select cases can be derived from blood counts, diagnostic paracentesis, serum amylase determinations and appropriate roentgenograms. Recent advances in

vascular surgical techniques and equipment have made it possible to save cases which previously could not have been saved. Improved antibiotic therapy now saves some people with injured colons from colostomies and multiple surgical procedures. The physician must remain ever vigilant lest he overlook associated injuries while concentrating his attention on one particular dramatic injury. He must push and push and push to avoid unnecessary delays as these critically ill patients pass from medical echelon to medical echelon.

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COMPLICATIONS OF SUPRACONDYLAR FRACTURE OF THE HUMERUS

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INTRODUCTION

Many fractures in children pose no special problem in diagnosis or treatment. With the great potential for growth and remodeling of the skeleton, varying degrees of displacement are often acceptable and anatomic reduction is not even desirable in some instances. Good results are usually obtained in children's fractures as a group, regardless of the criteria applied.

Supracondylar fracture of the humerus in children is perhaps the most obvious exception to these generalizations. In review of a number of series of reports on this fracture, certain complications are repeatedly seen. Only by recognizing the possibility of such complications can adequate countermeasures be taken. This paper will comment on some of the complications encountered by various authors in their treatment of 2197 cases of this fracture in children.

Changes of Carrying Angle of the Elbow

In a review of 705 cases of supracondylar fracture [2,7,11,14–16,21,22] a measurable change in carrying angle was found in 134 (19%) as compared with the normal uninjured elbow. Of these cases, 31 had an increased degree of carrying angle (valgus). Unless extreme, this is only a matter of a slight increase in the degree of normal angulation and is therefore not a cause of cosmetic deformity. It is not often a cause of functional impairment, and objects can easily be carried at the side.

The other 103 of these 134 cases (15%) had a decrease of carrying angle tending toward, or actually resulting in cubitus varus. This can be a very apparent cosmetic deformity and can interfere seriously with function in some occupations.

Epiphyseal injury with growth disturbance is no longer regarded as a very common cause of this deformity.

The deformity results from persistent unreduced medial angulation of the distal fragment, with resultant varus deformity, or from unreduced lateral angulation of the distal fragment, with resultant valgus deformity[15,22] (Figure 1). Unreduced rotational deformity of the distal fragment has little associated deformity externally as the rotation can be compensated for at the shoulder. Residual displacement in an anteroposterior or mediolateral direction has no effect on carrying angle, though extremes of displacement can cause a change in the terminal degrees of the arc of motion.

A typical case of residual medial angulation is shown in Figure 2. This 16-year-old farm boy complained of cosmetic deformity and of difficulty in carrying heavy

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objects, such as filled milk pails, on that side. Carrying angle was 18° varus as compared with 5° valgus on the uninjured side.

The benign effect of residual rotation is shown in Figure 3. This 11-year-old girl was left with marked residual rotational deformity by x-ray films. Residual angulation, however, was minimal. There was a carrying angle of 5° on this side, compared with 8° on the uninjured side. She had no complaints either as to looks or function.

Simple displacement of moderate degree without angulation is also compatible with good results. A 4-year-old girl was left with residual posteromedial displacement of the distal fragment as is seen during healing, Figure 4. When examined at age 17, she had no complaints related to the elbow. There was a full range of motion with no change of carrying angle. New films showed great remodeling of the fracture site and there was little difference between the injured and the uninjured extremity.

Circulatory Complications

Varying degree of circulatory embarrassment of the extremity is common following supracondylar fracture of the humerus. This is usually satisfactorily resolved by reduction of the fracture. Conservative treatment in traction may be continued even in the absence of a radial pulse if capillary circulation appears to be intact and there is no great pain, no motor or sensory deficit, and no clinical evidence of increased pressure in the compartments of the forearm.

Fig. 1—Failure of reduction of angulation of the distal fragment with cubitus varus or cubitus valgus deformity resulting.

Fig. 2—Cubitus varus deformity in a 16-year-old boy. Supracondylar fracture with failure of reduction of medial angulation of the distal fragment.

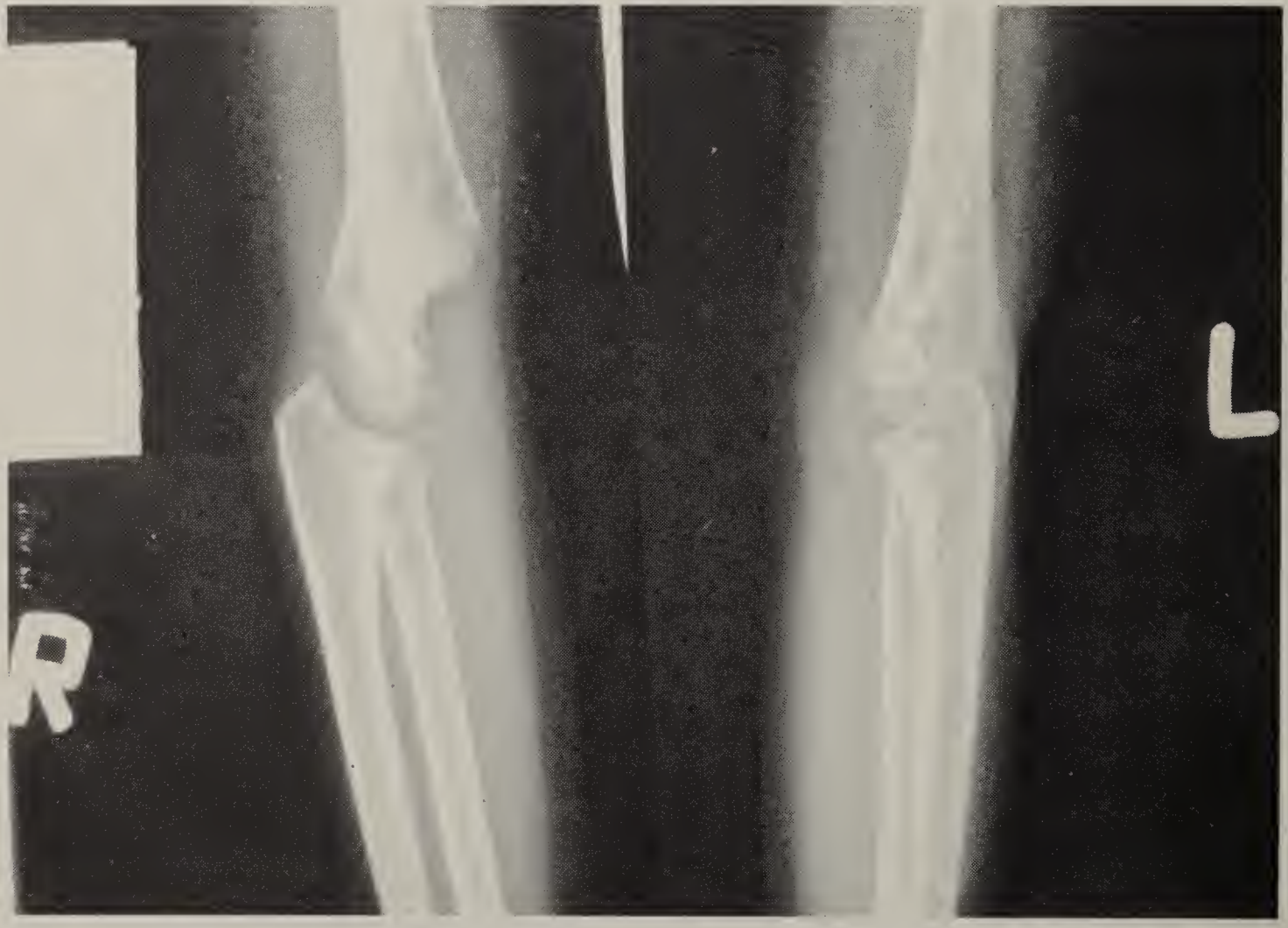

Fig. 3—The right elbow shows marked residual rotational deformity. There is no external cosmetic deformity and no appreciable change in carrying angle.

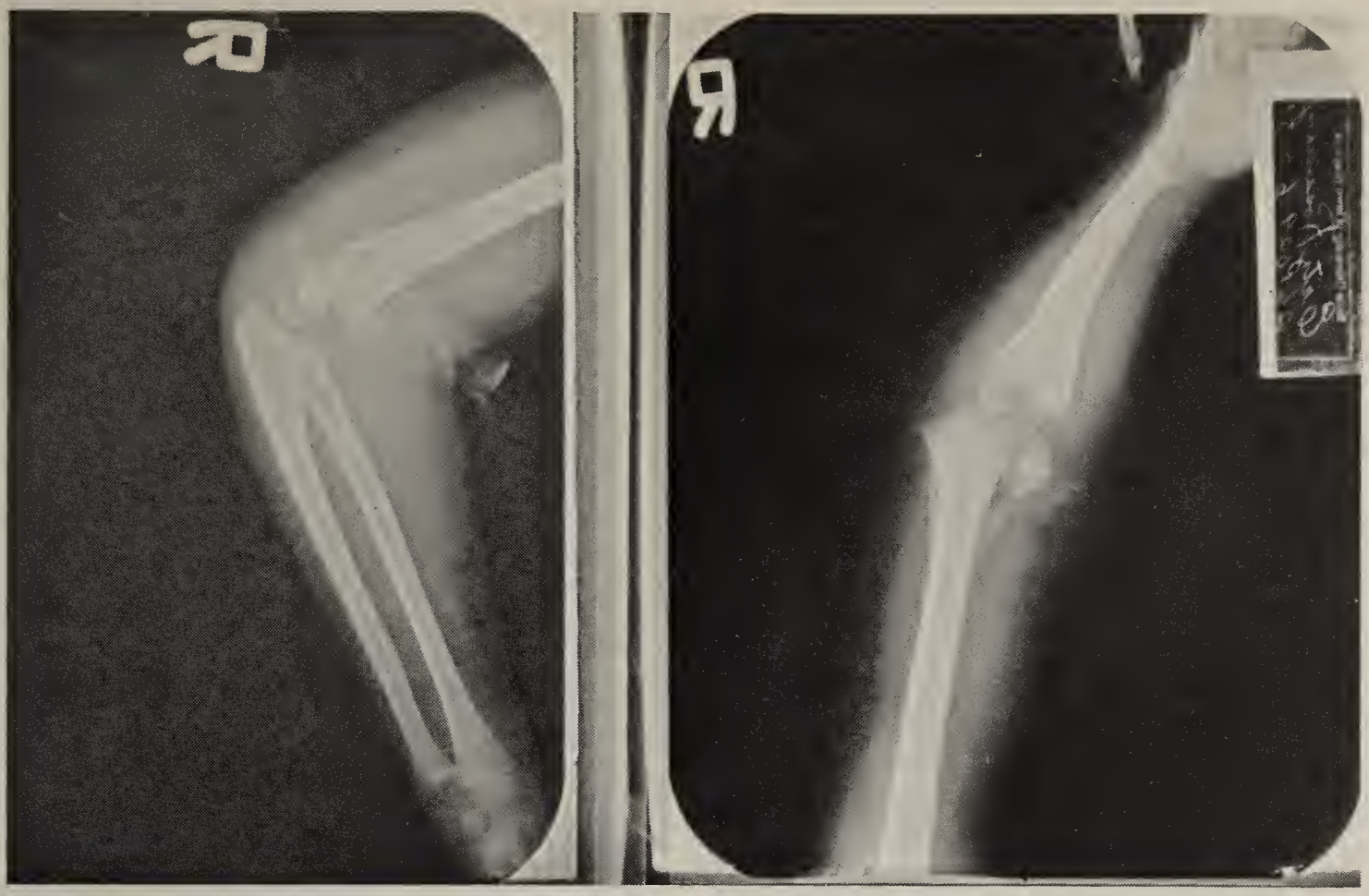

Fig. 4—Posteromedial displacement of the distal fragment as seen during healing. There was no external deformity after healing.

In 799 fractures[6,7,9,13,16,20,21] there were 26 cases of circulatory complication and 5 Volkmann's ischemic contractures as a result.

In cases of more extensive circulatory embarrassment, the five P's (pain, pallor, pulselessness, paresthesia, and paralysis) continue after reduction of the fracture. These are the hallmarks of impending Volkmann's ischemic contracture, the most disastrous of all complications of supracondylar fracture of the humerus.

The primary lesion is injury to the brachial artery, with secondary spasm of collateral arterial channels. Of the eight cases of impending contracture explored in one series[13], two had thrombosis of the artery, one had bone impingement, two had local spasm of the artery, two had rupture of the artery, and in one a bone fragment had impaled the artery.

Another group[24] of three patients with vascular insufficiency after this fracture had antecubital exploration. In two, the proximal bone fragment was impinging upon the artery while in the other case the artery was completely severed. One of these patients recovered with no residuals, another had mild residuals, while the third (explored 18 hours after injury) had appreciable muscle involvement as a sequela.

The area of muscle infarct is in the form of an ellipsoid with the long axis along the line of the anterior interosseous artery with its midpoint slightly above the middle of the forearm. The greatest damage is to the flexor digitorum profundus and flexor pollicis longus, with muscles peripheral to this affected in lesser degree. The median nerve lies nearer the center of the infarct and is usually more severely involved than the ulnar[8,23].

The soft tissue injury secondary to the ischemia varies in degree. In any but the more mild cases, reconstructive surgery later may offer poor results, even in terms of salvage.

A six-year-old boy sustained a supracondylar fracture of his left humerus. Treatment was primary reduction and application of a long arm cast which was left in place for eight weeks. When the

cast was removed, the presence of a Volkmann's contracture was first noted. Treatment then was with splints and physiotherapy. Little improvement in function was noted.

He was first examined in our clinics at age 9, with complaints of impairment in many areas of function of the hand. The left elbow lacked 15° of complete extension, the wrist lacked 20° of complete extension. There were contractures of the proximal and distal interphalangeal joints of all fingers. A release of the flexor muscles from the medial epicondyle was done, with some small improvement in extension of the wrist and fingers. This was followed, again, by splinting and physiotherapy.

When he was last seen at age 16 (Figure 5) it was noted that when motion of dorsiflexion at the wrist was attempted that the already present contractures of the fingers were exaggerated and grip was quite weak. A wrist fusion to improve function was advised for a later date. After ten years of treatment, function was still markedly impaired.

The early recognition and early treatment of this complication takes first priority in care of this fracture!

Neurologic Complications (other than with Volkmann's contracture)

Neurologic deficit associated with supracondylar fracture of the humerus is usually transient in nature, but may take considerable time for return in some cases. The prognosis for complete return with conservative care is excellent, although surgical exploration of the nerve may be warranted in a few instances. In case reports totaling 1504 fractures, neurologic complications were among the factors discussed.[1,2,6,9,11,13,16,20,21] Of these cases, median nerve involvement was noted in 58, radialnerve involvement in 51, and ulnar nerve involvement in 17 as isolated lesions and in combination. Another less frequent complication is tardy ulnar palsy in some cases with increased cubitus valgus.[16]

One of these complications, median nerve injury, may be quite minimal and

Fig. 5—Volkmann's ischemic contracture. Marked impairment of function after ten years of treatment.

often is not detected without close examination. In a typical case, a 4½-year-old boy sustained a supracondylar fracture of his left humerus. The only neurologic deficit noted was a weakness of flexor digitorum profundus to the index finger (a common finding in the minimal injury). Due to marked swelling, initial treatment was with Dunlop's traction. By the time a posterior plaster splint was applied five days later, there was a complete return of function. The extremity was normal in every regard on repeat physical examination two years later.

A Vascular Necrosis of the Distal Fragment of the Humerus

The blood supply to the distal end of the humerus has been more thoroughly studied in the adult than in the child.[4] The main nutrient foramina are on the medial aspect of the shaft at the junction of middle and distal third. The descending branch of this main humeral nutrient artery reaches the epicondylar region on both sides. Arteries also enter the medial and lateral epicondyles medially and laterally respectively, as well as posteriorly. Arterial twigs have been demonstrated to enter the trochlea and capitellum from all these sources and anastomoses are free. Vessels also enter the condyles from the region of the olecranon fossa.

Idiopathic aseptic necrosis of the distal humeral epiphyses, presumably secondary to loss of blood supply, has long been a recognized entity. Panner described idiopathic avascular necrosis of the capitellum in papers in 1927 and 1929.[17,18] In the first of the three cases he described in 1929, the later x-ray films show changes *possibly* consistent with avascular necrosis of the trochlea as well. He did not describe these changes as abnormal; the trochlear ossification center is consistently irregular by x-ray and develops from several small foci.[3] Of further difficulty in the evaluation of the younger patient, the trochlear ossification centers are not seen until around age seven and there is a marked skewness in time of appearance in a group of individuals.[10]

Such aseptic necrosis may also appear after trauma not involving fracture, but with trauma definitely related to onset.

In 1940, Phemister[19] showed microscopic changes consistent with aseptic necrosis and creeping substitution following an elbow fracture with the capitellum and a portion of the trochlea as a displaced fragment. The underlying lesion in cases associated with fracture is loss of blood supply to the distal fragment as a consequence of vascular injury.

If collapse of soft, newly formed bone occurs in the area of creeping substitution during replacement of the avascular bone, the articular surface may be compromised and secondary osteoarthritic changes can result. The mechanism here

Fig. 6—A supracondylar fracture with marked displacement of the distal fragment. Blood supply to the distal fragment was compromised.

Fig. 7—The same elbow as in Figure 6, nine years later. Marked osteoarthritic changes; the original fracture did not involve the joint itself.

is *not* related to disruption of the articular surface itself at the time of injury.

The diagnosis may be difficult to make until the end result is evaluated years later. In a series of 53 cases, McDonnell[16] reports four patients with avascular necrosis of the trochlea following supracondylar fracture of the humerus (8% incidence). The true incidence may be even higher than this as the occurrence of this lesion is more widely appreciated.

A seven year old boy sustained a supracondylar fracture with rather great displacement (Figure 6). The fracture was reduced and held by skeletal traction through the ulna until early healing had occurred. There was a five degree loss of carrying angle but the result was excellent in function. When the patient was again seen at age 16 he had complaints of weakness of grip on that side, and of morning stiffness which disappeared with exercise. The alteration of carrying angle had not changed; though the elbow had measurable lessening of valgus the result was not cosmetically deforming. There was palpable crepitus on flexion or extension of the elbow. Films of the elbow (Figure 7) showed moderate osteoarthritic changes which were attributed to late effects of avascular necrosis. The original fracture did not directly involve the joint.

SUMMARY

Unlike many fractures in children, supracondylar fracture of the humerus may have a number of complications.

Complications encountered in a number of series of cases have been summarized and typical case histories are given.

Recognition of the possibility of a given complication is the key to proper treatment while time remains.

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MANAGING VASCULAR INJURIES OF THE LOWER EXTREMITY

Roger L. Mehl, M.D.[1]

INTRODUCTION

Commonly occurring in our fast-moving society are the resultant injuries sustained by sudden deceleration from high velocity speed. While automobile accidents are the prime contributor, industrial mishaps also result in a multiplicity of injuries, including frequent damage of a major blood vessel in an extremity.

Techniques for experimental vascular repair, first described by Carrel and Guthrie[4,12] over 50 years ago, have become routine in the treatment of degenerative arterial disease, but are relatively new in the field of acute vascular injury. It was not until the latter half of the Korean War that reconstruction of damaged arteries replaced ligation, a practice which had dominated the surgical scene since introduced by Ambroise Paré in the 16th century.[1,9] The results of this change were decisive. The rate of limb amputation following injury to a major artery, which had averaged over 50% at the closure of World War II,[5] decreased to 13% by the end of the Korean conflict.[13] More recent civilian series, with a shortened transportation time and lesser degree of soft tissue damage, report the amputation rates less than 4%.[18] Thus the practice of vessel ligation can no longer be justified except under the most unusual of circumstances.

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Examination

A cautious but expedient approach to diagnosis must be carried out to minimize unnecessary delay. The conspicious presence of a bony injury often results in an orthopedist being the first physician summoned. He must remain alert to the multiplicity of possible associated injuries. While the specialized skills of internist, urologist, neurologist and thoracic or vascular-oriented surgeon may be desirable, these specialists are often unavailable. The orthopedist is left to evaluate and institute the first measures of treatment.

Due to the sudden and often violent nature of the accident, and to the precarious general physical state of the patient, a history may be neither forthcoming nor of value. Important to assess, when possible, are the degree of cardiorespiratory, diabetes and renal disease and the extent of vascular insufficiency. An elevated blood urea nitrogen or blood sugar may imply kidney or diabetic disease and a friend's or relative's telling of a previous myocardial infarction or stroke is indicative evidence suggestive of atherosclerosis.

While an injured vessel may be conspicious when bleeding into an open

wound, it may no longer be obvious when there is complete division with retraction and cessation of bleeding, or when slow venous or arterial bleeding occurs into a closed wound. Only constant vigilance will ascertain the delayed developments of the latter.

Initial observation, especially when the patient is elderly, should define whether one is tending an acute or chronic lesion. Failure to recognize evidence of an acute arterial occlusion at a site removed from the area of atherosclerosis may lead to an irreversible degree of ischemic necrosis. While reconstruction should always be attempted, successful repair is often difficult or impossible. Conspicious signs of atherosclerosis include lack of hair on the lower legs and toes, atrophic skin, peripheral ulcerations and decreased skin temperatures. When the degree of resistance offered by a minimal elevation of the extremity produces pallor, the limb is receiving its blood supply mainly via collaterals. If venous filling is delayed greater than 20 seconds after the limb is replaced to the level position, the degree of insufficiency is severe. Should the limb now be placed in a dependent position, the decreased arteriolar pressure of the collaterals fails to drive the poorly oxygenated venous blood through the capillaries against the elevated venous hydrostatic pressure and cyanosis is observed.

Moderate to marked ischemia is characterized by paresthesia, hypalgesia, analgesia and loss of function of the small muscles of the feet and toes. The skin becomes acutely cyanotic, waxy and cold and there may be an absence of pulsation. The presence or absence of pulses can be misleading: they may be present in patients with a tangential laceration and associated hematoma, or appear absent to palpation when there has been significant blood loss with ensuing shock. Associated nerve damage may also produce anesthesia but a careful examination will delineate a discrete anatomical pattern of disfunction in contrast to the more diffuse pattern observed with ischemia.

The normal undamaged vessel carries a positive electrical charge on the outer wall and a negative charge along the inner intimal lining.[24] The intima is therefore capable of repelling the cellular elements in the blood which carry a similar charge of negativity. With injury to the intimal surface, as in contusion or laceration, the electrical polarity is reversed leading to a positive charge along the site of the disrupted intima. Cellular elements, including platelets, are now attracted to the injured surface. If thrombosis can be prevented, a thin film of fibrin will layer out along the intimal surface acting as an insulating membrane and causing the electrical polarity to revert to normal.[24] However, should an unusual degree of turbulence occur, as along a narrowed anastomotic line, fibrin will continue to layer out, incorporating red cells in its matrix, and eventually lead to obstruction of the lumen.

Acute trauma places the extremity, without pre-existent collaterals, into immediate jeopardy. With the blood flow which would normally ensure viability to the extremity, interrupted, there is immediate danger of tissue necrosis and eventual gangrene. This author[17] has experimentally shown the expected viability and function of the lower limb, following complete obstruction to the blood supply, to be 100% when recirculation is established within 6 hours. These results decrease to 66% and 0% after 8 and 10 hours, respectively, of room temperature ischemia.

A simple classification of arterial injury includes:

1. Transection of the artery
    a) complete
    b) incomplete
2. Tangential laceration
3. Fracture by acute hyperextension
4. Contusion with thrombosis
5. Occlusion of lumen by extrinsic pressure
6. False aneurysm
7. Arterio-venous fistula
8. Simple spasm

While the first 7 are obviously treatable by surgical means, considerable controversy surrounds the treatment of

vascular spasm. Some authors[18] even suggest pure, simple spasm to be non-existent.

While rarely encountered, true arterial spasm can be caused by blunt trauma and may simulate an arterial occlusion. If allowed to persist, spasm may offer impedance resulting in turbulence, reduced blood flow and possible thrombosis. Considerable delay may result from attempts with nerve blocks and vasodilators or in waiting for spontaneous resolution to occur. Pre-operative angiography can be misleading and rarely adds to the clinical examination or justifies the added ischemic interval. The delays may cost the patient his limb. Surgery is therefore indicated whenever there are physical findings suggestive of arterial damage.[2]

More commonly, spasm develops secondary to actual damage of the vessel wall—contusion. Sencert[21] delineated three forms of contusion: a. first degree, a fine crack in the intima; b. second degree, a disruption of the intima; c. third degree, disruption of both the medial and the intimal layers. All three forms may be caused by acute hyperextension or blunt trauma.

Treatment

While acute ischemia requires expedient surgical intervention, initial efforts must be directed toward saving the patient's life, with limb-saving a secondary goal. External hemorrhage, shock, airway obstruction and hemothorax or pneumothorax must first be considered and treated when found. Elderly patients, susceptible to hypotension if inadequate perfusion pressure exists for an extended length of time, may develop an acute vascular thrombosis or ischemia of a vital organ. Until it is possible to treat the peripheral vascular injuries, one should control hemorrhage with the application of a compression pack to the wound. Tourniquets should be avoided as they will block available collateral pathways. While preparing the patient, one must continually keep alert to the development of a gradually enlarging hematoma which might compromise an otherwise patent vascular supply. During surgery special care is required to prevent excessive instrumentation or retraction which might traumatize collateral vessels. Copious wound irrigation can markedly lessen wound contamination. Mobilization of local collateral vessels, both proximal and distal to the site of injury can offer enough mobility to afford direct anastomosis. Division of collateral branches should be avoided. Tempting as it may appear, resuturing a partially lacerated vessel will inevitably result in narrowing of the lumen. It is, therefore, best to first resect one-half to one centimeter of artery, both distal and proximal to the torn edge, trim the adventitia by drawing it over the cut end of the artery, (Figure 1), and follow by a subsequent re-anastomosis. This insures adequate removal of microscopically damaged intima which may later act as a site for thrombosis. Normally, distances of two centimeters or greater can be primarily re-anastomosed. Should the defect occur at a joint an even greater distance can be bridged by putting the limb in slight flexion. When primary anastomosis can not be performed, an autogenous saphenous vein graft, taken if possible from the opposite thigh, may be used to bridge the defect. To help prevent late aneurysm formation, this graft should be smaller in diameter than the vessel that it replaces. If there is a discrepancy in size, a sufficiently wide lumen can be made by first dilating the ends of the vessel atraumatically with a hemostat, or injecting saline into the closed vein under pressure. Arteries smaller than 6 mm should be repaired with interrupted mattress sutures of 6-0 silk or Tevdek.* This will evert the edges and prevent encroachment of the lumen. In larger vessels, everting sutures are used to triangulate the circumference, the repair then completed with a continuous layer of suture. (Figure 2) Constriction caused by undue tension will lead to a compromised distal flow and possible thrombosis. Synthetic prostheses, more readily available than autogenous vein

*Tevdek—J. A. Deknatel and Sons, Inc., Queens Village, Long Island, New York.

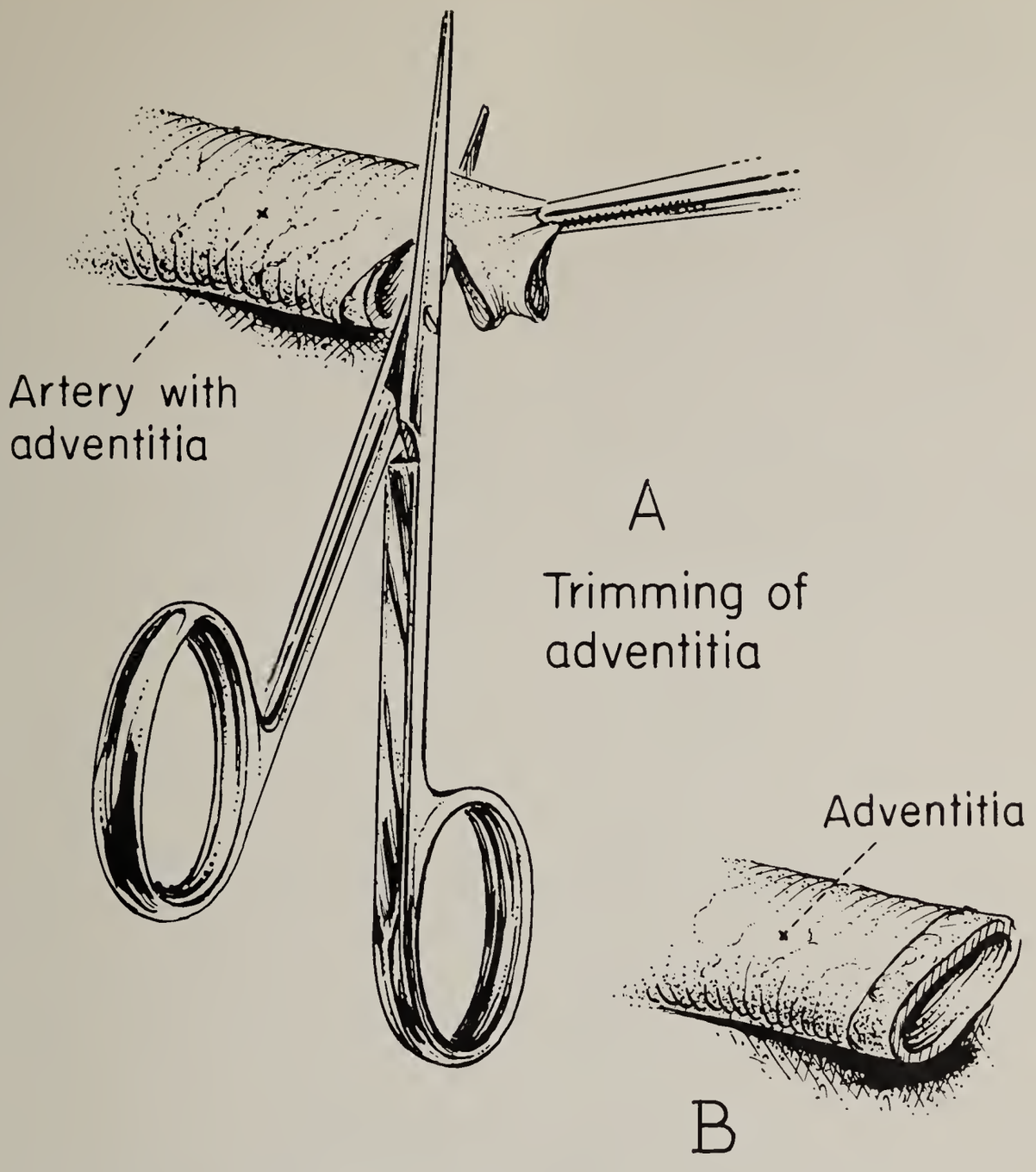

Fig. 1—(a) Trimming of adventitia (b) Artery after removal of adventitia

grafts, are best avoided because of their tendency to buckle at points of flexion and their frequent tendency to develop thrombotic occlusion in a contaminated field.[2,8] An arteriogram performed on the operative table should answer any question as to the adequacy of the repair. Where possible, the repair is covered with viable musculature and the wound closed primarily.

A pulsating hematoma, *false aneurysm*, when auscultated, produces a systolic bruit whereas a machinery-like murmur is classical for the presence of an arteriovenous shunt. Surgical repair of these is indicated immediately upon making the diagnosis.

Vascular Injuries With Fractures

Femoral injuries: In its long superficial course through the adductor canal, the superficial femoral artery frequently becomes damaged by fracture fragments, extrinsic penetrating trauma or crushing injuries. In addition, the vessel has a propensity, in the elderly, to become involved by obliterative arterial disease. Therefore, restoration of arterial continuity may still result in an insufficient blood supply, necessitating eventual amputation. Femoral vessels very rarely become involved by intertrochanteric fractures or fractures of the femoral neck. Mid-femoral fractures, however, may cause vascu-

lar damage by posterior dislocation of the distal fragments. The profunda femoris is a most difficult artery to repair if injured, because of its depth. Although rarely involved in proximal-third femoral fractures, it is treated no differently than vascular injuries in other locations.

Popliteal injuries: These are usually produced by closed fractures or dislocations of the knee. The popliteal artery or its collaterals may also be damaged by supracondylar or lower third fractures of the femur. Causes for the high incidence of injury to the popliteal artery are its superficial position, proximity to bone and the anchored position at the bifurcation. Distortion to a degree which might be minor to other areas of the vascular anatomy may be sufficient in the popliteal region to cause spasm, thrombosis or rupture of the vessel.

Treatment of these injuries carries a poor prognosis because of the frequent pre-existence of atherosclerosis and the inadequate collateral circulation about the knee region.[15] However, in the event of obstruction to the main channel these collaterals may provide the minimal quantity of blood to maintain viability until definitive repair can be accomplished. Whereas obstruction to many peripheral arteries would not be limb-threatening, the patency of the popliteal artery is critical to the survival of the

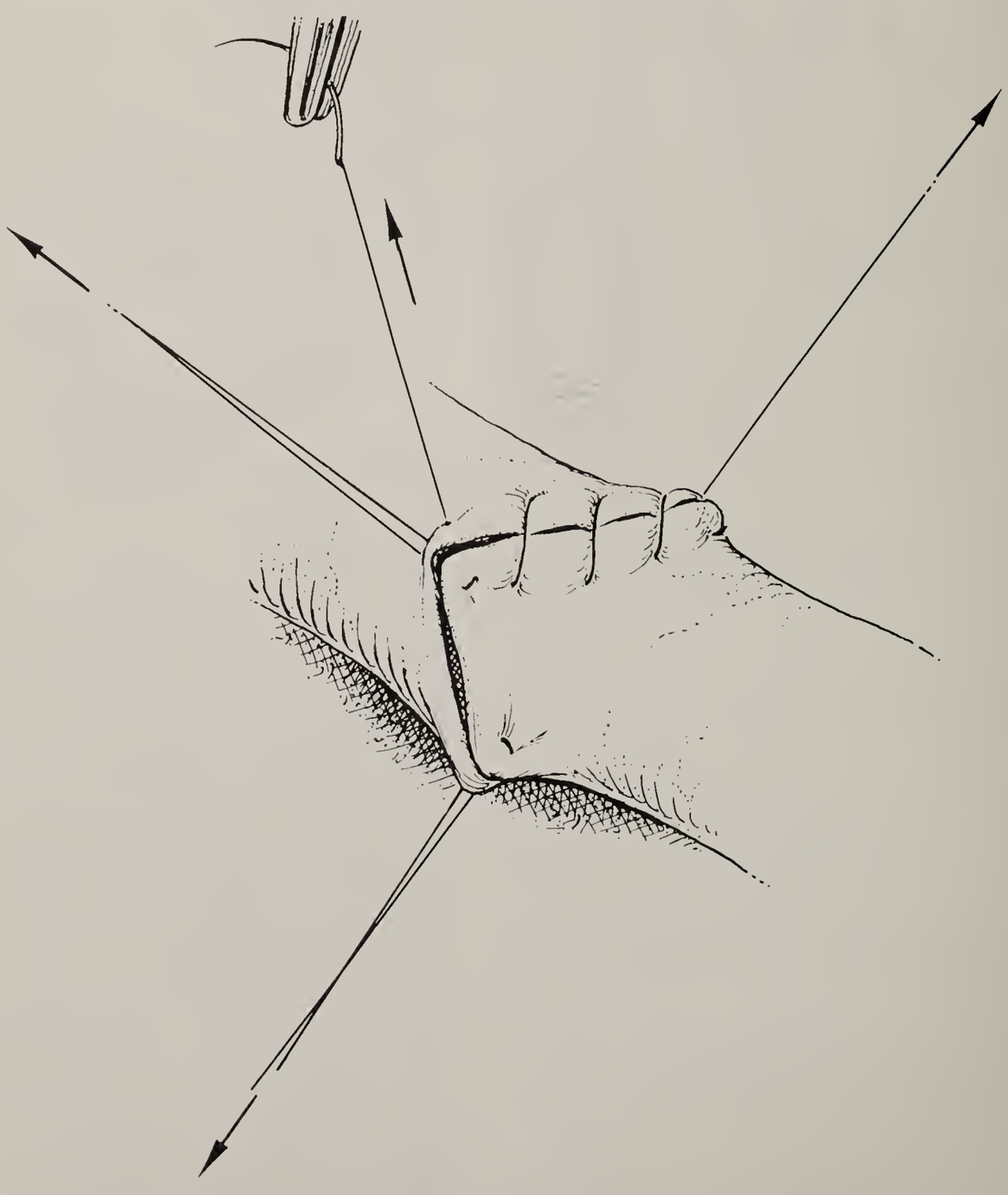

Fig. 2—Repair with a continuous layer of suture

lower leg. Ligation of this vessel in World War II resulted in a 72.5% amputation rate.[5]

Tibial injuries: The severity of injuries to the anterior and posterior arteries follow quite a different course: Puncture of an anterior tibial artery may be caused by the sharp spurs of a fractured tibia. Rarely amenable to repair, it may be ligated with a minimal morbidity. In contrast, ligation of the posterior tibial artery in the elderly results in gangrene in greater than 50% of the cases.[10] Thus all effort must be expended to carry out a satisfactory repair in such situations.

When bone injury co-exists with an arterial lesion it should be treated simultaneously with the arterial surgery. If severe comminution of the fracture is present it may be advantageous to achieve stability of the fracture site before performing the arterial repair. Surgery should be performed in this order, however, only if it causes no undue delay to the vascular repair. The procedure of choice for femoral fractures is intramedullary nailing. This provides the stability to guard against re-dislocation of the fracture or disruption of the vascular anastomosis. Nails or screws used to provide internal fixation of lower limb fractures will allow earlier mobilization of the extremity and diminish incidence of phlebothrombosis and muscle atrophy.

Post Operative Care

The greatest vigilance must be observed in the early post operative period for the development of a thrombosis at the anastomotic site. An apparently successful anastomosis may develop an occlusion due to a lowered blood pressure or flow, to an increased platelet adhesiveness,[11] or to a continued electrical adhesiveness at the site of the intimal disruption. Compression of a femoral artery by callus formation at the site of the healing fracture has been reported to cause obstruction weeks after the repair.[19]

Deep vein thrombosis secondary to peripheral venous obstruction may be caused by external compression of bone fragments, from a hypercoagulability state due to increased fibrinogen formation in response to products of tissue damage,[6,23] or from immobilization by an overly tight plaster cast. Prolonged bed rest may lead to a decreased cardiac output and to a significant increase in spontaneous thrombosis of other organ systems, notably the renals and cerebral vessels.[7] When deep thrombosis occurs, it has the potential of converting a relatively minor co-existing fracture and vascular injury into the catastrophe of a pulmonary embolism.

Prophylactic measures to prevent venous thrombosis include: immediate bivalving a cast after application; avoidance of unnecessary immobilization; elastic stockings; deep breathing exercises in the early post operative period; and early ambulation where possible. Sympathectomy and intra-arterial vasodilators have little success and anticoagulants are of limited value in delaying intra-arterial clotting because of the rapidity of the blood flow.[20] They can, however, be effective in delaying progressive intravenous clotting when blood remains in a static state. Due to the possibility of early wound bleeding, anticoagulation should be delayed for the first 24 hours.

An osteofascial compartment such as the calf, made tight by progressive edema, may obtain beneficial relief by a fasciotomy. Intermittent hyperbaric oxygenation has also been used until adequate collateral circulation develops.[22]

Heat and cold should not be used directly on the extremity. Heat increases the degree of metabolism to exceed the available vascular supply. Cold causes vasoconstriction and progressively greater ischemia.[3] Julian,[16] however, has suggested application of a heating pad to the abdominal wall to facilitate blood flow by dilating, reflexly, the vessels in the peripheral area.

Broad spectrum prophylactic antibiotics are suggested for all patients with open wounds. A prolonged, intensive program of physiotherapy is usually a necessary requirement in the rehabilitation of these patients. When applicable, frequent iso-

metric contraction exercises of the quadriceps, dorsal flexors and plantar flexors should be taught to, and performed by, the patient in bed.

When obvious failure of the vascular repair occurs in the elderly with severe co-existent atherosclerosis, a necessary amputation should be performed rather than risk the patient's life with severe gangrene and sepsis.

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THE EDITOR'S PAGE

Accidents occur in the United States at the rate of one every 26 seconds in the automobile and one every 8 seconds in the home.

All aspects of a hospital are patient oriented and this applies with special emphasis to the emergency room where a battered patient arrives and places his complete trust in the medical competency of the hospital. The necessity for prompt professional ambulance service to the emergency unit, the need for specialized centers which can immediately bring vital services to the injured patient, the perplexing problems of staffing the over-burdened emergency room are currently the subject of considerable public and newspaper interest and are directly related to the planning necessary for care of the injured patient. Some hospitals are fortunate that they can immediately call upon teams of specialty surgeons necessary to care for any patient with multiple injuries.

Second only to patient care is the education of medical students, interns, residents and paramedical personnel and this is the most enduring and tangible products of our efforts. They will carry this learning to other emergency units whether it be the damp jungles of Vietnam, a small town along a superhighway or the busy casualty room of an urban medical center. It is for them that the surgeons have enjoyed writing this Symposium on Trauma.

Francis M. Howard, M.D.
Guest Editor

BYTERIAN-ST. LUKE'S HOSPITAL MEDICAL BULLETIN

PRESBYTERIAN-ST. LUKE'S HOSPITAL

MEDICAL BULLETIN

VOL. 7 NO. 2 APRIL 1968

Immunoelectrophoresis and Ultracentrifugation Techniques in the Biochemical Laboratory

Pacemaker Exit Block Modified by Vagus

The Wrist in Relation to Ulnar Drift

Achilles Tendon Reflex

Abstracts

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VOL. 7. NO. 2 APRIL 1968

TABLE OF CONTENTS

page

58 **Some Uses of the Immunoelectrophoresis and Ultracentrifugation Techniques in the Clinical Biochemistry Laboratory**
ANATOLY BEZKOROVAINY, Ph.D.

64 **Vagal Modification of Exit Block from a Subsidiary Pacemaker Focus**
PAUL D. LEVIN, M.D. and RICHARD A. CARLETON, M.D.

69 **The Wrist in Relation to Ulnar Drift of the Fingers in Rheumatoid Arthritis**
JULES S. SHAPIRO, M.D.

75 **Achilles Tendon Reflex in Normal Human Subjects**
GYAN AGARWAL, Ph.D., BRADLEY BERMAN, M.D., MICHAEL HOGINS, PETER LOHNBERG, and LAWRENCE STARK, M.D.

94 **Abstracts and Reviews**

SOME USES OF THE IMMUNOELECTROPHORESIS AND ULTRACENTRIFUGATION TECHNIQUES IN THE CLINICAL BIOCHEMISTRY LABORATORY

ANATOLY BEZKOROVAINY, Ph.D.[1]

INTRODUCTION

Immunoelectrophoresis and ultracentrifugation are valuable tools in the clinical chemistry laboratory. Several limitations of these methods must, however, be recognized, the most serious being that only qualitative data can be obtained from them. The two methods are of most value in recognizing circulating immunoglobulin abnormalities, although useful information can be obtained regarding other serum proteins or the proteins of other biological fluids.

A number of pathological conditions encountered in clinical practice are accompanied by qualitative or quantitative changes of the serum, cerebrospinal fluid[2], or urinary protein content. The oldest and perhaps the simplest method to study protein changes in serums is the A/G ratio determination, which is based on the fact that albumin-like proteins are soluble in 50%-saturated $(NH_4)_2SO_4$ solutions, whereas the globulin-like proteins are not. A more sophisticated method of protein fractionation, commonly used in the clinical laboratory is zone electrophoresis, performed either on paper or cellulose acetate membranes. Proteins are permitted to separate on the supporting medium under the influence of an electric field and on the basis of their individual electric charge at a specified pH-value (usually 8.6) for a certain period of time, and are subsequently visualized by staining the supporting medium in a dye solution. Such electropherograms are then subjected to "quantitation" either by densitometry or elution-colorimetry. Serum is usually separated into the γ, β, α-2, α-1, and albumin fractions by this method, and deviations of any of these fractions from normal levels are of diagnostic value. However, only the albumin fraction may be considered to be a pure protein in the chemical sense. Thus some constituents of the β-globulin fraction are transferrin, hemopexin, plasminogen, and β-lipoprotein, whereas some constituents of the α-2 fraction include haptoglobin, ceruloplasmin, α-2 macroglobulin, and erythropoietin.

Immunoelectrophoresis is the best method yet developed for the analytical resolution of complex protein mixtures. The technique is based on the initial separation of a protein mixture by zone electrophoresis using agar gel as the supporting medium. Follwing the electrophoretic separation, a narrow trench is cut parallel to the path of protein migration and is filled with an antiserum to the protein mixture or to a specific component of the mixture. The antigens and

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[2]Abbreviations used:
IEP—immunoelectrophoresis, CSF—cerebrospinal fluid, S—Svedberg units

antibodies are then permitted to diffuse toward each other, and precipitin arcs then appear in locations possessing the optimum antigen-antibody concentrations. As a rule, the higher molecular-weight proteins diffuse slower than the lower molecular-weight ones, and the corresponding precipitin lines will, therefore, appear close to the antigen path of migration. This group of proteins includes the IgM and α-2 macroglobulins and the β-lipoprotein. Precipitin arcs corresponding to proteins with relatively low molecular weights (e.g. albumin and transferrin) will be found closer to the antibody containing trench. Normal human serum is separable into some 30 distinct components by this method. However, in a routine IEP analysis using commercial human serum antiserum, only 11 components are unequivocally identified. A typical IEP pattern is shown in Fig. 1.

LIMITATIONS OF THE IMMUNOELECTROPHORESIS METHOD

In spite of the high resolution capabilities of the IEP technique, several shortcomings must be kept in mind when performing and examining the results of an analysis.

a. The antigen and antibody concentrations of the specimens and antiserums employed must be within certain specified ranges. Otherwise, conditions known as antigen or antibody excess occur with considerable blurring or even absence of expected precipitin lines. The antiserums available commercially are designed to give good patterns with some 10 μl of normal human serum if the IEP procedure is performed by a standardized procedure on a microscope slide. Conditions of antigen excess may occur if the serum presented is hypergamma-globulinemic. The situation can be corrected if such specimens are serially diluted. The antibody excess situation occurs if an extremely dilute specimen is analyzed. One remedy would be to dilute the antiserum. However, it is more convenient to concentrate the specimen until its protein content is in the range of that of normal human serum. Concentration of samples must usually be performed when an IEP pattern of a CSF or urine sample is desired. Thus, since the normal protein concentration in CSF is some 45 mg%, one would require some 6 ml of this fluid to obtain 0.1 ml of a 3g% sample, which would be reasonably suitable for either the IEP or zone electrophoresis procedures.
b. The evaluation of an immunoelectropherogram is often complicated by the sheer number of precipitin lines one sees. If the clinician is interested in the state of a specific protein of a biological fluid, it is then advisable to perform additional analysis using antiserum prepared specifically against the protein in question. Antiserums of good quality to the immunoglobulins, albumin, transferrin, ceruloplasmin, and β-1-C globulin are commercially available.
c. It is sometimes difficult to decide if a precipitin line present in a patient's serum and apparently absent in a normal serum is due to the presence of an abnormal protein, or is simply due to an increased level of some serum component normally present in very low amounts. The question can often be resolved by using antiserums specific to the suspected "minor" component, if such antiserum be available. Frequently, however, other diagnostic methods must be employed to resolve such findings.
d. IEP is a qualitative tool, and the results with respect to a specific component of a biological fluid, in addition to the general appearance of the precipitin line, can be reported only as apparently absent, decreased, slightly decreased, normal, slightly increased, and increased.

STRUCTURE OF IMMUNOGLOBULINS

The IEP method is most useful to the clinician in connection with the various immunoglobulin disorders. Before de-

scribing the role of the IEP and ultracentrifugation methods in the diagnosis of these conditions, it would be advisable to present a brief review of the elements of immunoglobulin structure. Four types of immunoglobulins are presently recognized on the basis of their chemical, physical and immunochemical properties: IgG, IgA, IgD and IgM. These account for some 80, 13, 1, and 6% of the total human serum immunoglobulin content respectively (a total of 1500 mg%). The first three types have a molecular weight of 150,000-160,000, whereas IgM has a molecular weight of nearly 1,000,000. The three smaller immunoglobulin molecules consist of two heavy (H) chains (molecular weight of 55,000 each) and two light (L) chains (molecular weight of 20,000 each), and these four chains are held together by a combination of disulfide linkages and noncovalent bonds. The IgM molecule apparently consists of an aggregate of the basic 4-chain units. The L-chains are common to all four immunoglobulin types, however, two types of L-chains (termed the Kappa and Lambda chains) can be distinguished immunologically. Normal immunoglobulins contain both the Kappa and Lambda chains in a 2:1 ratio. The H-chains found in each of the four immunoglobulin types are not related immunologically, and the differences observed among these proteins are thus due to differences in the physical-chemical properties of their H-chains. A partial immune cross-reactivity among the four immunoglobulin types is observed when serum antiserum is used in the analysis, and this is due to the identity of their L-chains. However, specific antibodies to each of the four immunoglobulin types can be prepared by using the isolated H-chains as the immunizing agent, or by absorbing the antiserum prepared to a specific immunoglobulin with a mixture of the Kappa and Lambda chains (frequently a mixture of Bence-Jones proteins of the two types, see below).

MULTIPLE MYELOMAS

A condition termed multiple myeloma develops when a group of plasma cells (clones) exhibits malignant proliferation and synthesizes an immunologically inactive protein called paraprotein or M-protein. The L-chains of the paraprotein are of either the Kappa or the Lambda type, but not both. The H-chains are immunologically related to any of the four normal H-chain categories, and myelomas can thus be classified as being of the IgG, IgA, IgD, or IgM type. The latter is frequently termed Waldenstrom's macroglobulinemia, or primary macroglobulinemia. Two additional types of multiple myeloma are recognized whereby the pathologic serum contains paraproteins of low molecular weight. These are the H-chain disease and the IgL myeloma. The H-chain disease is characterized by the uncontrolled synthesis of H-chains that are immunologically inactive and apparently incapable of combining with the L-chains. On the other hand, serum from patients with IgL myeloma contain large amounts of free L-chains of either the Kappa or Lambda type with no apparent abnormality of the H-chains found in the fully formed immunoglobulins. Of all plasma cell malignancies encountered in clinical practice, IgG Myeloma accounts for 55.7%, IgA for 19.8%, IgM for 18.9%, and IgL for 6.4%. IgD myeloma and H-chain disease have been encountered three times each.

The usual clinical-chemical identification of these diseases begins with a report of a hyperproteinemia and a low A/G ratio. Zone electropherogram shows a very sharp dense zone in the γ or β-globulin area, indicating the presence of a paraprotein. The final identification is then made by the IEP and/or ultracentrifugal methods, which can classify the paraproteinemia with respect to the six types described above. Multiple myeloma associated with the IgG paraprotein shows depressed IgA and IgM serum levels. The IgG line developed by either whole serum antiserum or by its specific antiserum is extremely heavy, highly curved, and frequently shows bizarre precipitin patterns (fig. 1). In the ultra-

centrifuge, the 7 S component is greatly elevated, and remains very sharp (low degree of diffusion) throughout the run. IgA myeloma serum shows depressed IgG and IgM levels with drastically elevated IgA component shaped much like the IgG paraprotein precipitin line. Ultracentrifugal analysis shows elevated 7 S component and additional components with S-values between 7 and 19. These "abnormal" peaks disappear and the 7 S component is even more elevated if the ultracentrifugation is done in the presence of mercaptoethanol. IgM myeloma is characterized by low serum IgG and IgA levels and a drastically elevated IgM-like component. The IgM line is frequently irregular. Ultracentrifugal analysis reveals a marked elevation of the 19 S component, and frequently, the presence of heavier (24-32 S) proteins. Paraproteinemic serums will frequently exhibit precipitin lines that are not found in normal serums and which coalesce with the IgG, IgA, or IgM lines. These "abnormal" lines are usually due to the presence of free L-chains (Bence-Jones proteins) in the patient's serum. Myeloma of the IgL type is accompanied by greatly elevated L-chain serum levels. Since no H-chain abnormality exists, specific antisera to IgG, IgA, and IgM are of little help, although a decrease in any or all of these may be noted. IEP pattern developed by whole serum antiserum may show an abnormal line in the γ- or β-globulin region, which may coalesce with any of the immunoglobulin lines. Zone electrophoresis, however, shows the presence of a typical paraprotein. Ultracentrifugation shows normal or slightly decreased 7 S and 19 S components and an increased 4.5 S peak. Thus the presence of a paraprotein in zone electropherograms and no change or slightly decreased levels of the 7 and 19 S components in the ultracentrifuge are strongly suggestive of the IgL myeloma.

BENCE-JONES PROTEINS

A specific protein, called the Bence-Jones protein, appears in the urine of 30-50% of patients with multiple myeloma. This protein is precipitated by heating acidified urine to 50-60°C and is redissolved by raising the temperature to boiling. The Bence-Jones proteins have been identified as being the L-chains of the paraproteins present in serum, and their immunologic type is either Kappa or Lambda. It must be noted, however, that normal urine contains small amounts of the normal immune globulin L-chains (a mixture of Kappa and Lambda types). However, these are usually not detectable if the urine is not greatly concentrated prior to analysis.

PRIMARY AND SECONDARY HYPERGAMMAGLOBULINEMIAS

Blood immunoglobulin levels are increased in a variety of pathological conditions (e.g., hepatitis), and these conditions are frequently called secondary hypergammaglobulinemias or polyclonal gammapathies. The immunoglobulins present are fully active immunologically and appear as heavy diffuse zones in zone electropherograms. IEP reveals increased levels of one or all immunoglobulin types, whose precipitin arcs are, with respect to their shape, not much different from those found in normal serums. Paraprotein hypergammaglobulinemias, often termed primary hypergammaglobulinemias or monoclonal gammapathies, are characterized by very narrow dense zones in zone electropherograms and decreased functional serum immunoglobulin levels. IEP reveals a heavy sickle-shaped precipitin line of the IgG, IgA, IgM, or IgD type, the other immunoglobulin precipitin lines being very faint or altogether absent. It would thus seem that primary and secondary hypergammaglobulinemias should be easily distinguishable. Yet conditions do arise where a decision is difficult to make, especially if one deals with the early stage of multiple myeloma. The diagnosis may frequently be made by employing antiserums to the Bence-Jones proteins (L-chains of the Kappa and Lambda type) in the immuno-

electropherogram. If the hypergammaglobulinemia is of the secondary type, antiserums to both the Kappa and Lambda-type Bence-Jones proteins will show increased levels of the component in question. If primary hypergammaglobulinemia is present, only one antiserum will show a heavier precipitin line with the immunoglobulin in question. The precipitin line developed by the other Bence-Jones protein antiserum will usually be fainter than that developed with control serums or will be altogether absent. However, even the use of Bence-Jones protein antiserums may not give conclusive results, and the diagnosis must then be based on other information.

β-1-C GLOBULIN

The examination of a serum for the β-1-C component by the IEP method is frequently used to aid in the diagnosis of lupus erythematosus. The β-1-C component is a part of the "complement" system, and its levels are greatly depressed during the acute stages of the disease. Its levels return to normal during remissions. The β-1-C component is transformed into the β-1-A component upon storage of the serum sample, and the latter form is inactive if assayed for "complement" activity. β-1-C levels are also frequently depressed during acute glomerular nephritis.

OTHER BIOLOGICAL FLUIDS

IEP patterns of CSF are often requested by the physicians. As pointed out above, CSF has to be concentrated, some six ml being required for a meaningful analysis. In most instances, the clinician is interested in the IgG levels, since its elevation above the 1.25-2.0 mg% mark is strongly indicative of multiple sclerosis. It is the author's opinion that zone electrophoresis with a reliable quantitation of the electrophoretically separable fractions is better suited for the diagnosis of this condition than is the IEP method.

Urine specimens may be analyzed by the IEP technique for a variety of rea-

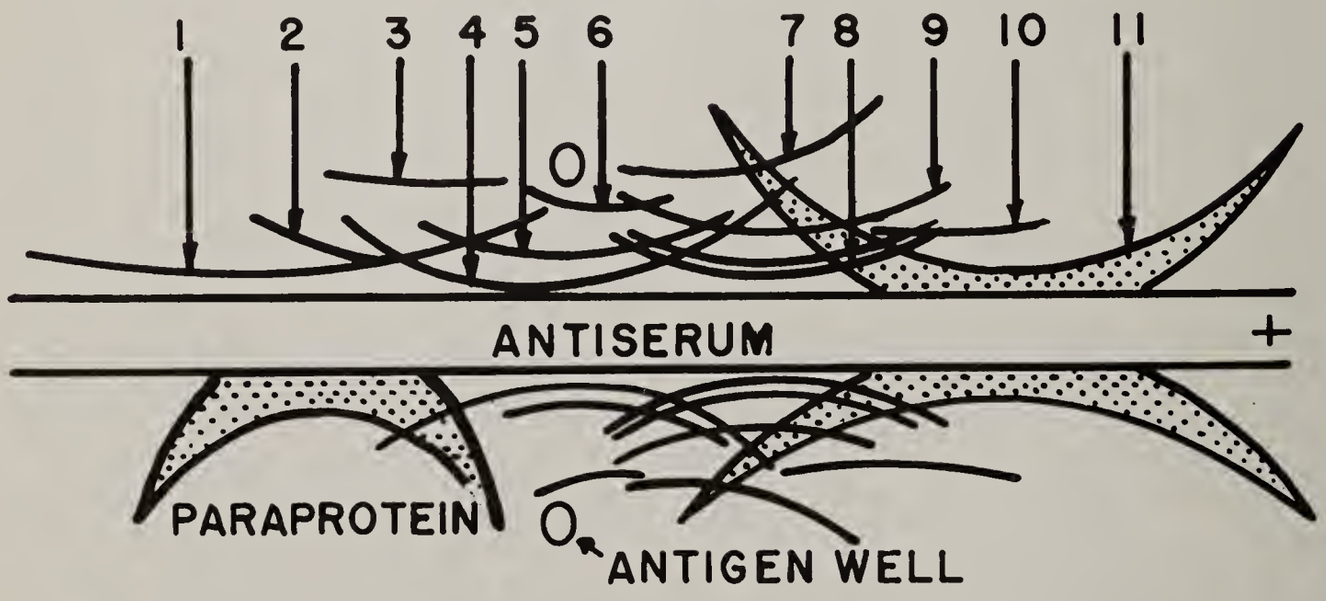

Fig. 1.—Immunoelectrophoretic pattern of a normal serum sample (upper) and that of a paraproteinemic serum (lower). The individual components are marked as follows:

1. IgG
2. IgA
3. IgM
4. Transferrin
5. βIc. βIa globulin
6. βI-lipoprotein
7. α2-macroglobulin
8. Haptoglobin complex
9. Ceruloplasmin
10. αI-glycoprotein
11. Serum albumin

Notice the absence of IgA and IgM in the paraproteinemic serum.

sons. Thus the urine of patients with multiple myeloma may contain a Bence-Jones protein which may then be identified as to its type by employing antiserums to the Kappa and Lambda-type Bence-Jones proteins. Patients with kidney diseases excrete a variety of serum proteins in their urine. The clinician can usually get some idea as to the extent of glomerular damage by the nature of serum proteins in urine: the presence of albumin and or transferrin in urine may be indicative of relatively mild damage, whereas additional presence of macroglobulins (e.g. IgM or γ-2 macroglobulin) may designate severe glomerular difficulty.

QUANTITATION OF INDIVIDUAL PROTEINS

IEP, as indicated above, is a qualitative method of analysis. The electrophoretically separable zones of a zone electropherogram can be quantitated; however, these are only mixtures of several individual protein components. Quantitation of a specific protein can be performed by the so-called single diffusion method. Antiserum to the protein in question is incorporated into molten agar, which is poured into a suitable container and permitted to solidify. Wells are then cut in the agar and are filled with the appropriate standards and the test serum. After a suitable period of time, precipitin rings will appear around the wells containing the antigen. The diameter of the precipitin ring is then proportional to the logarithm of the concentration of the protein in question in the test serum. Kits containing the necessary components for the quantitation of the immunoglobulins, the β-1-C protein, transferrin and ceruloplasmin are commercially available.

THE ROUTINE IMMUNOELECTROPHORETIC ANALYSIS

The IEP analysis performed in the Biochemistry Department is designed to examine the immunoglobulins and the β-1-C component of the biological fluid submitted. The technical aspect of the method involves the analysis of the serum, CSF, or urine sample with whole serum antiserum and antiserum specific to IgG, IgA, IgM, and the β-1-C component. The report notes qualitatively any apparent deviations in the levels of these four proteins from those of normal controls, the presence of precipitin lines not present in normal control samples, and any peculiarities in the shape of the precipitin lines. Quantitation of individual proteins is not performed. The physician should be free to request an examination of the state of any protein other than the above four in the specimen submitted, providing the appropriate antiserum is available commercially. Zone electrophoresis on cellulose acetate strips with quantitation by the elution-colorimetry method may be done as a part of the IEP procedure upon request. Ultracentrifugation of specimens will be done after special consultation of the physician with a member of the Biochemistry Department.

VAGAL MODIFICATION OF EXIT BLOCK FROM A SUBSIDIARY PACEMAKER FOCUS*

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Richard A. Carleton, M.D.**

In 1918, P. D. White presented the case report of a 49-year-old minister with rheumatic heart disease who had complete A-V block and a nodal pacemaker with intermittent 2:1 exit block.[1] This phenomenon was again noted in 1942 in a digitalized patient by Langendorf and Katz.[2] Vakil,[3] in 1955 reported a case of complete A-V block in which an idioventricular pacemaker was present and 2:1 exit block was postulated because the pulse rates were either 28 or 14 over a two day span.

We have had the opportunity to observe a patient with complete A-V block in whom the ventricular pacemaker intermittently had a 2:1 exit block which was modifiable by vagal activity. The patient was treated with an implanted electronic pacemaker for the consequences of the exit block.

CASE PRESENTATION

This 30-year-old Panamanian born housewife entered Presbyterian-St. Luke's Hospital complaining of a slow pulse of four years' duration. She had come to this country 5 years prior to admission. Her past medical history was entirely negative except that she had been told at the age of 20 that she had "chronic nephritis." During her first and only pregnancy, at age 25, she was told that her pulse was abnormally slow. Eight days after an uneventful delivery, while walking, she suddenly fainted for a few seconds.

Over the next four years the patient experienced gradually decreasing exercise tolerance because of dyspnea, palpitations, and "pressing" substernal chest pain. During the six months preceding admission she experienced two brief episodes of syncope. She was referred for further evaluation.

Physical examination revealed a well-nourished young woman in no acute distress. Her blood pressure was 210/70 millimeters of mercury. Her pulse rate was 38 per minute with dropped beats and her respiratory rate was 16 per minute. Jugular venous pressure was estimated at six centimeters of blood. "A" waves were noted in her neck at the rate of 64 per minute. Her lungs were clear to percussion and auscultation. The cardiac apex was diffuse in the fifth and sixth intercostal spaces two centimeters to the left of mid-clavicular line. The first heart sound varied markedly in intensity. The second heart sound was normal. Atrial sounds were audible. A Grade III/VI systolic ejection murmur

*Kindly supplied to us by Dr. Lewis Woodruff, Joliet, Illinois.

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was best heard in the second left intercostal space. All peripheral pulses were normal and there was no peripheral edema.

Admission hemogram was normal as was her admission urinalysis. A serum creatinine was 1.7 milligrams percent and her 24 hour creatinine clearance was 39 milliliters per minute. The patient had a negative complement fixation for Chaga's disease. A biopsy of the left atrial appendage, performed at the time of pacemaker implantation, was normal.

At the time of admission, a catheter was inserted into the right ventricle for temporary pacing. Pacing was conducted intermittently between studies of her arrhythmia. Seventy-two hours after admission, a permanent epicardial pacemaker system was implanted on the left ventricle. At the time of thorocotomy a serous pericardial effusion was encountered. Studies of this fluid, including guinea pig inoculation, were negative. Subsequent renal biopsy showed healed glomerulonephritis.

The clinical diagnosis at discharge was complete A-V block, etiology unknown.

ELECTROCARDIOGRAMS

An electrocardiogram taken in 1962* (Fig. 1) showed a sinus nodal rate of approximately 55 per minute, second degree A-V block and two types of QRS complexes. One occurred independently of the atria at a rate of 38 per minute (A); the other occurred intermittently 0.18 second after P waves (B), including after a slightly premature atrial systole in lead I. Complexes of type A had a duration of 0.15 second and a contour resembling those of right bundle branch block. The conducted complexes (B) also had a duration of 0.15 second, had left axis deviation, and also had a large secondary R wave in the right precordial leads.

Her electrocardiogram on admission (Fig. 2) revealed complete A-V block and sinus rhythm which exhibited marked variation in the P-P interval. This atrial arrhythmia was neither related to respiration nor to ventricular complexes. The ventricular rate was 43 per minute. The QRS complexes produced by this focus appeared to be the same as the nonconducted impulses (A) of 1962. Intermittently, the interval separating QRS complexes abruptly doubled, from 1.4 to 2.8 seconds (E in Fig. 2). This phenomenon of 2:1 exit block was studied. Neither vigorous respiration nor Valsalva maneuver changed the exit block. However, a statistically significant change was produced by massage of either the left or right carotid sinus. Exit block occurred spontaneously on the average once out of every 12 beats; with massage, exit block occurred once every four beats (Fig. 3A, $P<.02$). Atropine was then given in two doses of 0.2 milligrams IV. This produced a marked sinus tachycardia at a rate of 155 P waves per minute (Fig. 3B). The ventricular rate accelerated to 65 per minute with a third type of QRS complex (C). This slowed over two minutes until a beat occurred (F, Fig. 3C) with a contour intermediate between the antecedent and subsequent complexes. The subsequent QRS complexes were similar to the original complexes, but now had a rate of 55 per minute with no evidence of exit block (Fig. 3D). Several hours later, still another focus assumed control at a rate of 35 per minute (Fig. 3E). This persisted until the permanent electronic pacemaker was implanted two days later (Fig. 3F).

INTERPRETATION AND COMMENTS

Atrioventricular conduction was possible in 1962 when a P wave followed the preceding QRS complex by more than 1.12 seconds, or when a P wave occurred 0.45 second after the preceding QRS complex (3rd complex, lead III, V6, Fig. 1). This suggests an A-V nodal system refractory period of approximately 1.1 seconds and a brief phase of supernormal A-V conduction occurring about 0.45 second after ventricular depolarization. No tracing taken in 1966 showed impulses conducted through the A-V node. The non-conducted QRS complexes appear to arise from the same

focus in 1962 and in 1966. Initially, 2:1 exit block was sporadically imposed on this ventricular pacemaker. The increased frequency of the exit block during carotid sinus massage and the increase in rate of this initial ventricular pacemaker focus to 55 per minute after atropine suggest that vagal fibers were acting on this pacemaker. Moreover, the occurrence of a different, relatively rapid, idioventricular discharge, which terminated with a fusion complex between the two foci (F, Fig. 3C) after atropine suggests the probable existence of a vagal effect on some segment of the autorhythmic Purkinje cells within the ventricles.

The origin and route of the ventricular depolarization sequences are unclear.

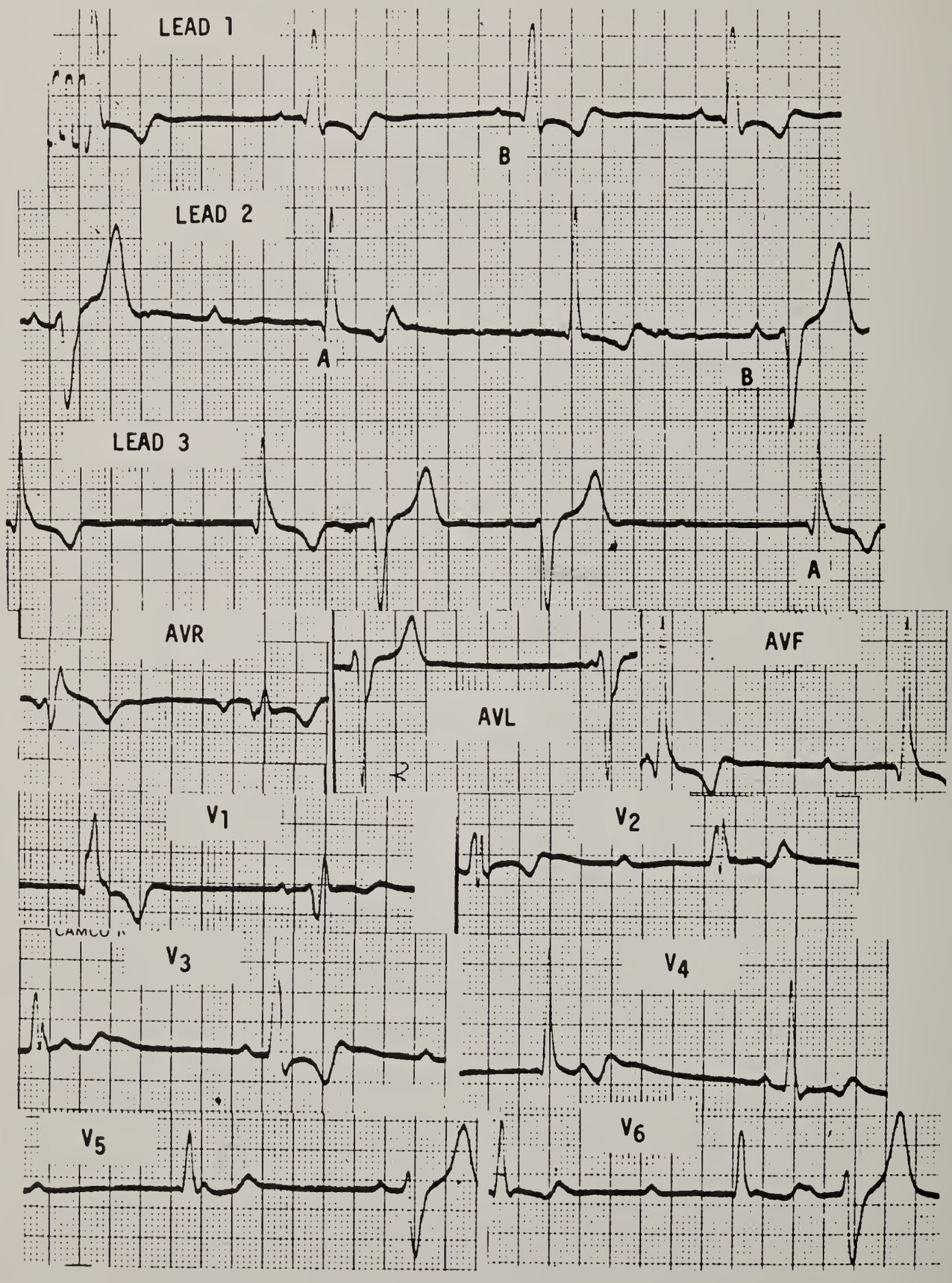

Fig. 1.—Electrocardiogram taken on February 27, 1962

The QRS complexes which were initiated through the A-V node in 1962 are grossly abnormal. Their contour suggests complete right bundle branch block and abnormal conduction in one of the divisions of the left bundle system.[4] The QRS complexes of the dominant pacemaker in 1966 were totally different in contour, suggesting either a different route of impulse entry or a different site of impulse initiation.

Accentuation and abolition of the exit block by vagal stimulation and suppression respectively suggest that the dominant pacemaker of 1966 may have been in the A-V nodal system. However, for this to be true, one must postulate two different routes of ventricular depolariza-

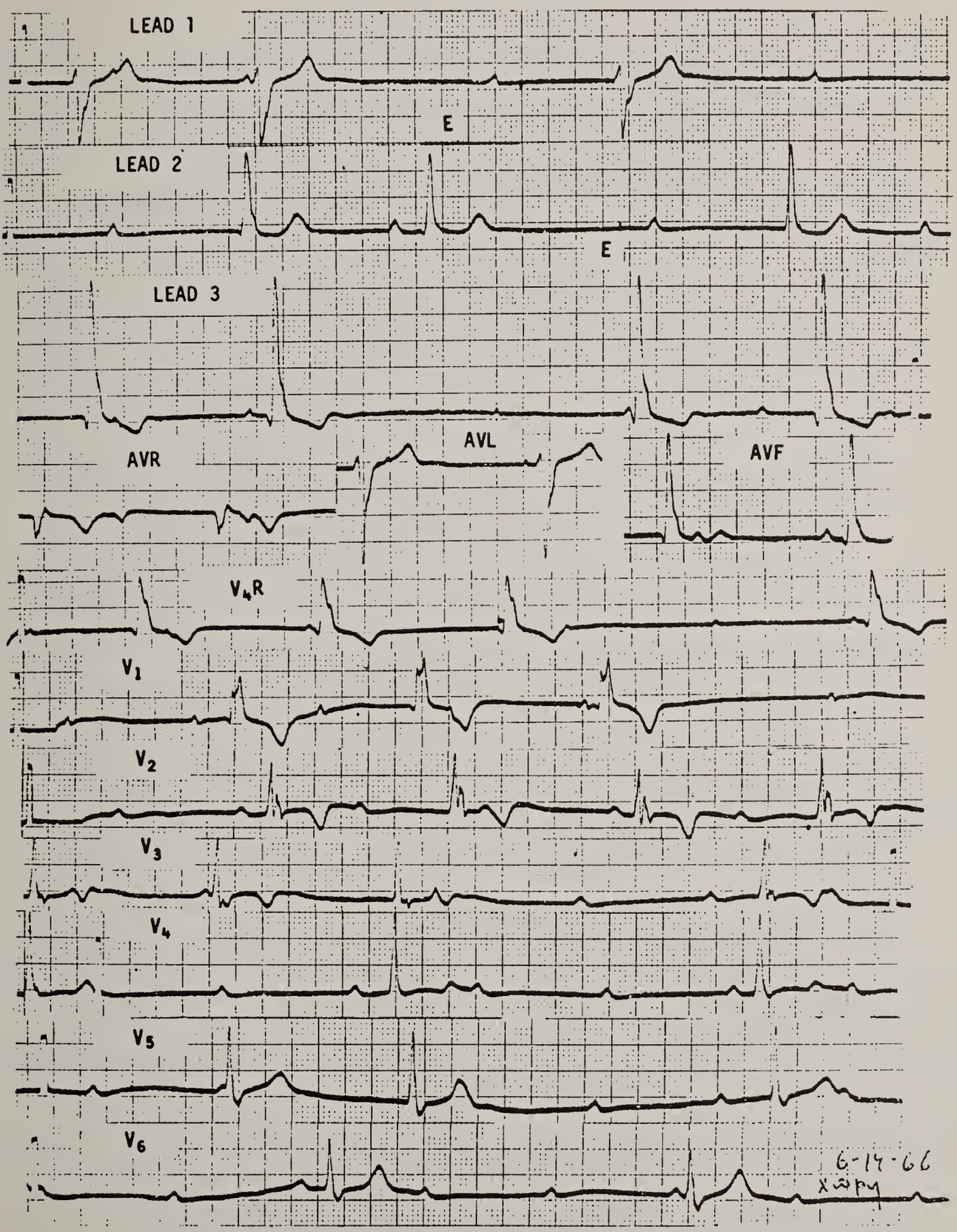

Fig. 2.—Electrocardiogram taken on June 14, 1966.

tion for impulses originating in the A-V nodal system. Since rate did not determine the mode of ventricular depolarization, these two routes would have to be anatomically distinct. The bundle of His and the paraspecific fibers of Mahaim might be the two postulated routes of egress from the A-V node.

An alternate hypothesis is that the dominant ventricular pacemaker of 1966 was in the Purkinje network and that this idioventricular pacemaker was subject both to exit block and to acceleration by parasympathetic blockade. Evidence that autorhythmicity of idioventricular foci was influenced by acetylcholine in this patient was afforded by the idioventricular focus which accelerated sufficiently after atropine to assume control briefly. Vagal fibers are shown to reach the ventricles,[5] probably to modify ventricular function,[6] and to change the rate of idioventricular pacemakers.[7] These considerations lead us to suggest that the patient had exit block from an idioventricular pacemaker focus.

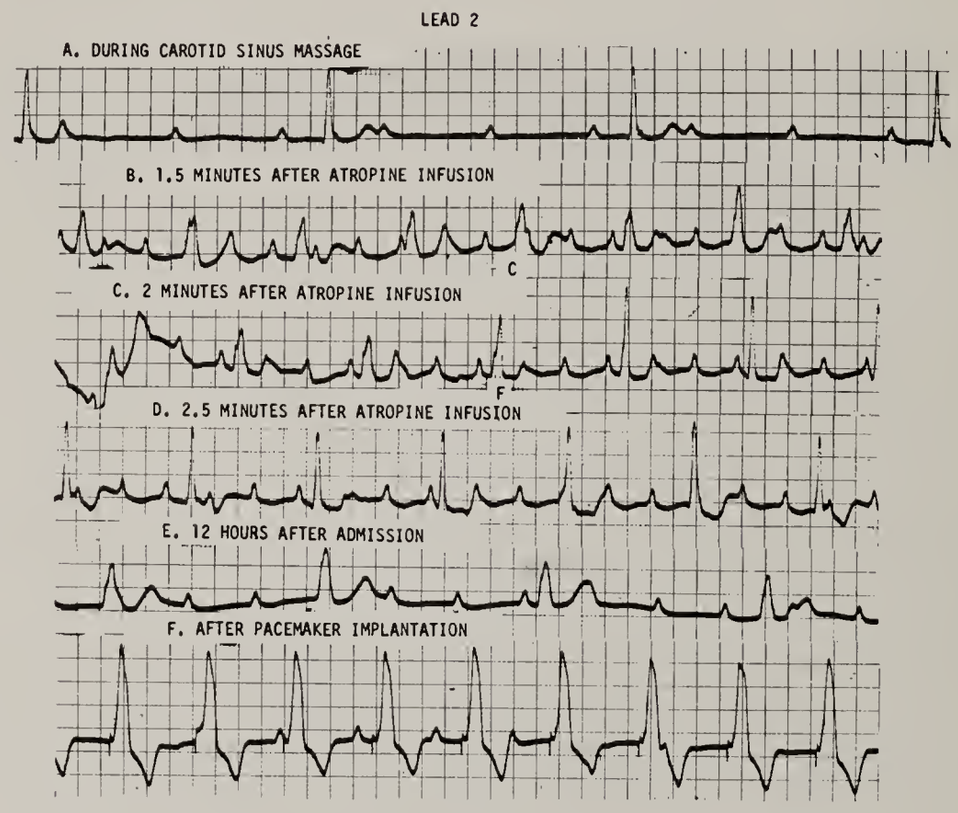
LEAD 2
A. DURING CAROTID SINUS MASSAGE
B. 1.5 MINUTES AFTER ATROPINE INFUSION
C
C. 2 MINUTES AFTER ATROPINE INFUSION
F
D. 2.5 MINUTES AFTER ATROPINE INFUSION
E. 12 HOURS AFTER ADMISSION
F. AFTER PACEMAKER IMPLANTATION

Fig. 3.—Electrocardiograms. Strips A-D taken on June 14, 1966; Strip E taken on June 15, 1966; Strip F taken on June 17, 1966.

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THE WRIST IN RELATION TO ULNAR DRIFT OF THE FINGERS IN RHEUMATOID ARTHRITIS

Jules S. Shapiro, M.D.[1]

INTRODUCTION

The etiology of ulnar phalangeal drift has been the subject of much work in the past. However, the fact that different authors ascribe primary importance to a multitude of factors merely underlines the lack of knowledge of the true precipitating mechanism. Indeed, as Brewerton[1] has stated, "One of the primary reasons for studying ulnar drift has been the failure to understand its cause."

Gravity, functional usage, effects of disease on the metacarpal phalangeal joint structures, and accentuation of normal anatomy and function at these joints have all been investigated as important factors in this deformity.

In the course of a definitive study of the natural course of the rheumatoid hand[9], it became apparent to investigators at the Rheumatism Foundation Hospital, Heinola, Finland, that another factor seemed to be present in almost every x-ray showing ulnar phalangeal drift. This factor was a deviation of the metacarpals radialward with a rotation of the carpus radialward. A review of the literature revealed but a brief mention of the radial carpal rotation of the rheumatoid wrist[3,6] and a most casual reference to the association of this deviation with ulnar phalangeal drift.[5] A study of this relationship has begun in order to substantiate it and to study its mechanism. In this brief report there are presented roentgenographic and clinical examples to substantiate this relationship.

The x-rays taken at the Rheumatism Foundation Hospital, Heinola, Finland, are uniquely suitable for attempting to validate such an association. All hand films of the past fifteen years were taken in a standard manner as described by Soila.[8] Therefore, one can compare position on two films taken years apart with relative certainty. Clinical material substantiated the findings. The following cases are roentgenographic and clinical examples of this combination of deformities.

CASE REPORTS

Case 1. A. O.: male, 56 yrs., when first x-ray was taken in 1956. Carpal destruction has begun, but no rotation has occurred (Fig. 1A). By 1962, rotation has progressed but there is as yet no sign of phalangeal drift. Note position of trapezium in relationship to radial styloid compared to first x-ray (Fig. 1B). By 1966, the rotation has increased still further, with the carpus rotated radially and the metacarpals deviated radially. In the interim, ulnar phalangeal drift has occurred (Fig. 1C). The clinical picture at this time was the characteristic one of prominence of the second metacarpal head and straightening of the ulnar border (Fig. 1D).

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Fig. 1A, B, C, D.—Case 1.

Case 2. T. A.: male, 39 yrs., when first x-rayed in 1961 (Fig. 2A). Note position of radial styloid and trapezium, denoting radial rotation. In a film taken five years later, radial rotation has increased slightly but now ulnar phalangeal drift is also seen (Fig. 2B). A clinical photograph at this time shows prominence of 2nd metacarpal head and straightening of the ulnar border (Fig. 2C).

Fig. 2A, B, C.—Case 2.

Case 3. E. L.: female, 43 yrs., when first x-rayed in 1955. No carpal rotation is noted, but intercarpal narrowing is present (Fig. 3A). By 1962, the rotation and deviation have become extreme (Fig. 3B). 1966: marked ulnar phalangeal drift. Note the relationship of the trapezium and radial styloid (Fig. 3C). A photograph taken at this time once again shows findings as in preceding cases, namely, prominence of 2nd metacarpal head and straightening of ulnar border (Fig. 3D).

Fig. 3A, B, C, D.—Case 3.

Case 4. G. K.: In x-rays taken in 1956 the carpus is normal bilaterally (Fig. 4A). By August, 1961, rotation has occurred bilaterally, but no phalangeal drift is seen (Fig. 4B). X-ray film of May, 1962, shows drift to have occurred in the left hand but not in the right hand (Fig. 4C). The last x-ray taken October, 1962, five months later, shows both hands to have ulnar phalangeal drift (Fig. 4D). (The patient died of lupus erythematosus a short time later.)

Fig. 4A, B, C.—Case 4.

Fig. 4D.—Case 4.

DISCUSSION

At the time of filming, it is relatively easy to place a hand on an x-ray film in a position of radial or ulnar deviation, despite a relatively standardized x-ray technique. However, when the finding of ulnar or radial deviation is invariably present, and when a large series of standardized x-rays are reviewed, and all show radial wrist rotation with or prior to ulnar phalangeal drift[7], a certain degree of credence must be paid to these findings. Certainly, as one reviews the articles which have been written concerning this phenomenon (ulnar drift), almost all show the radial rotation and deviation described in their illustrative material.[2,4]

SUMMARY

That the two phenomena are associated seems to be quite well established. The problem that now remains is twofold: to find out what initiates the radial wrist rotation, and to determine how the wrist rotation exerts its influence on ulnar phalangeal drift. It is hoped that this short report will stimulate some thinking aimed toward solving this interesting problem.

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ACHILLES TENDON REFLEX IN NORMAL HUMAN SUBJECTS

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INTRODUCTION

Achilles tendon reflex in normal human subjects is quantitatively studied from the view-point of multi-input, multi-output systems theory. Isometric and isotonic reflex have been elicited in the gastrocnemius-soleus muscle in order to study the relationship between the initial conditions (muscle tension or length), the stimulus (hammer force) and the reflex response (change in foot torque or angle). In the isometric case, foot torque response is shown to be strongly related to hammer force, whereas the time at which the maximum foot torque response occurs is shown to be a function of initial foot torque. In the isotonic case with no external loading, the foot angle response is strongly related to hammer force and a plateau in the response is observed. In the isotonic case with external loading, the foot angle response is strongly related to involuntary initial foot angle as well as the hammer force.

I. Introduction

Since the Second World War, a great deal of attention has been paid to problems of human engineering, particularly in situations where a human operator is part of a process control loop. The analytical treatments of such situations have been made using the concepts of both steady-state and transient analysis and of stochastic process theory (1, 2, 3, 4, 5). As the knowledge of neurophysiology has been extended, primarily from animal experimentations under anesthesia, a large measure of success has been achieved in these human engineering studies. The fact remains, however, that a great many rather simple questions about the human motor coordination system remain unanswered.

The elucidation of the spinal reflexes by Sherrington and his followers (6)

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undoubtedly forms a major block of information on which our conceptions of the motor system were built. His studies of isolated reflexes beautifully demonstrated the "wired in" patterns of reflex response which were present in his decidely non-physiologic "spinal cat" preparations. The experimental methods used for his work were designed to stabilize the reflex responses by the exclusions of any cerebral and cerebellar control or modulation of the reflex mechanisms. The medical research done on reflex activity in humans has been primarily from the point of view of clinical diagnosis (7, 8).

Achilles tendon reflex has been studied mainly as a diagnostic aid in patients with myxedema, neurosyphilis, hemiplegia and other diseases (9-21). All these investigators have been concerned with the measurement of half-relaxation time—time between the tap on the tendon and the moment when the muscle has relaxed halfway, and comparing this time in patients and in normal persons. Little or no attention has been given to the amplitudes of the input hammer force and the reflex response. The purpose of this study of achilles tendon reflex is to carry out a quantitative analysis of the reflex response from the viewpoint of multi-input and multi-output systems theory. Our ultimate goal is to inquire into the nature of the cerebral and cerebellar control of reflex activities by which these seemingly stereotyped responses are molded into a very versatile and adaptive motor coordination system.

II. Experimental Design

These experiments are designed to demonstrate the variation of myotatic reflex activity with the "programming" of a task under conditions of identical muscle length and tension. The two tasks are:

1. The maintenance of a position (muscle length) against a constant or varying force. This is basically a postural type of movement and may be viewed as, (a) feedback loop with error detection by the muscle spindle and a constant set point fixed by cerebrum or cerebellum, or, (b) a feed forward portion of a larger postural system with error detection by inner ear or vision.
2. The maintenance of a constant force (muscle tension) against a moving or static object. Monitoring in this case should be by golgi tendon organs and/or touch sensors with cerebral processing of the data including differencing against a reference from memory for error detection, with output directly from motor cortex without the need for a muscle length stabilizing mechanism.

III. Description of Ankle Tester

The subject was placed in the kneeling position with the lower leg horizontal and a brace anterior to the knee. The sole of the foot was fixed with straps to a plate which was arranged to rotate plantarflexion and dorsiflexion about the axis of the ankle joint. The rotation could be locked in certain anatomical positions for isometric experiments. The achilles tendon was struck by a hammer which was free to rotate about a fixed axis. A schematic diagram of the apparatus used is shown in Figure 1.

The angular position of the foot plate was measured via a potentiometer. The force exerted by the subject tending to rotate the foot plate was measured by four strain gauges attached to the side arms of the plate and connected in a bridge circuit. The output of the strain gauge bridge circuit was amplified with a d.c. differential amplifier. The force pulse input to the achilles tendon was measured by two strain gauges attached to the hammer. These strain gauges were connected in a bridge with two resistors of 330 ohms each and the output of the bridge was amplified with d.c. differential amplifier.

The electrical activities (electromyogram—EMG) of the anterior tibial muscle (ATM) and the gastrocnemius-soleus muscle (GM) were obtained using surface electrodes. The electrical signal

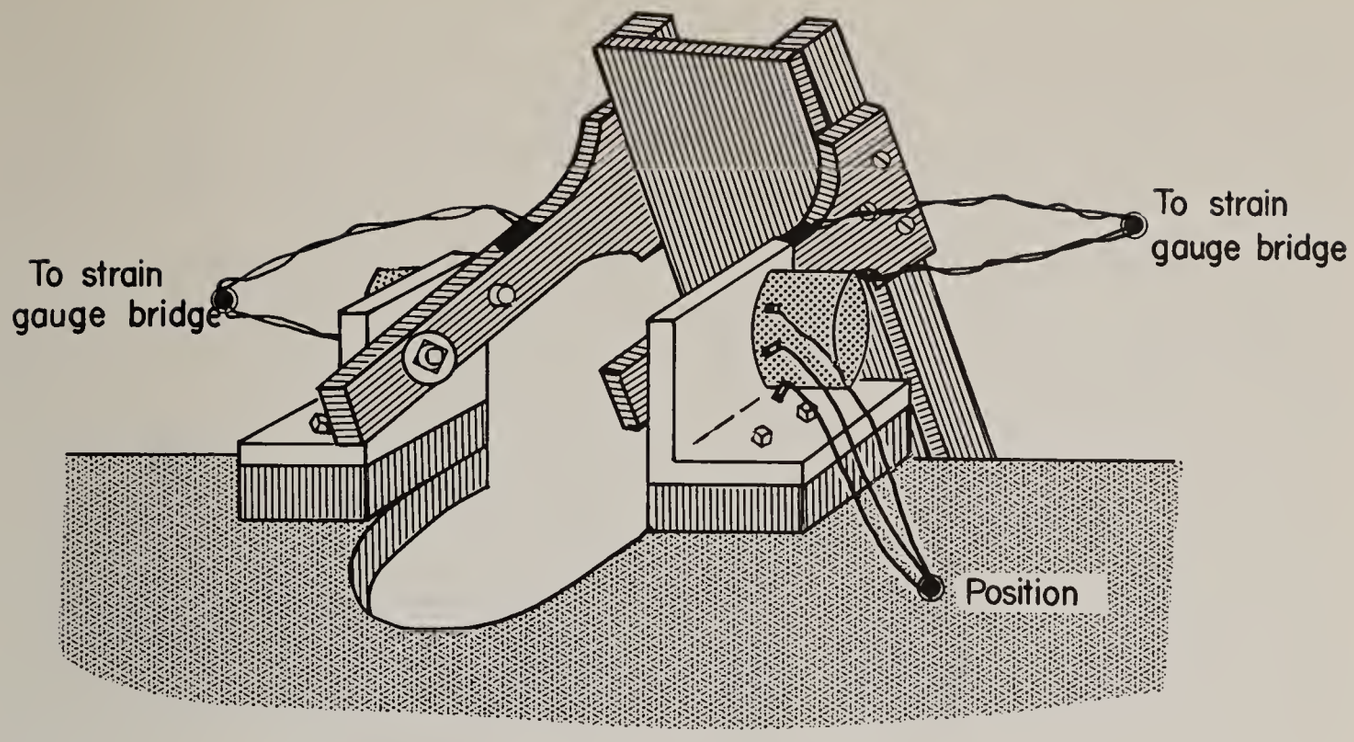

Fig. 1(a).—Schematic Diagram of Foot Plate.

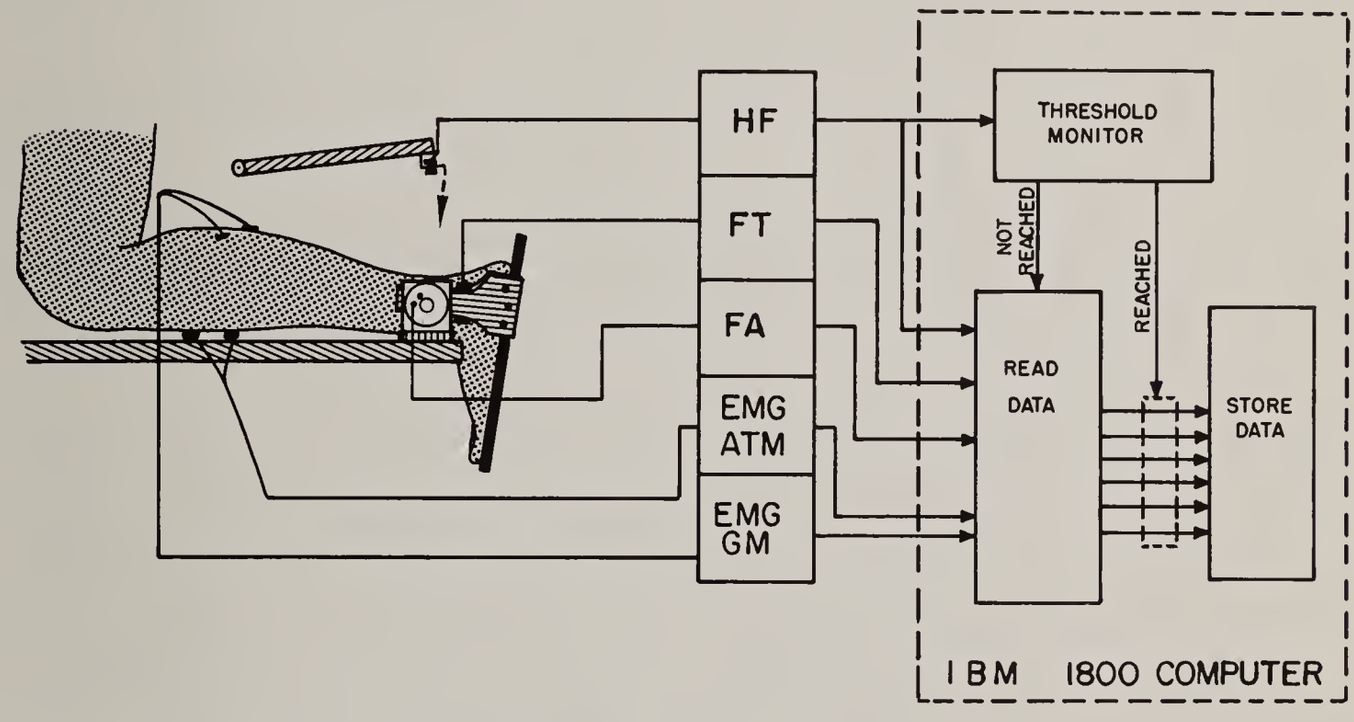

Fig. 1(b).—Schematic Diagram of Ankle Tester.

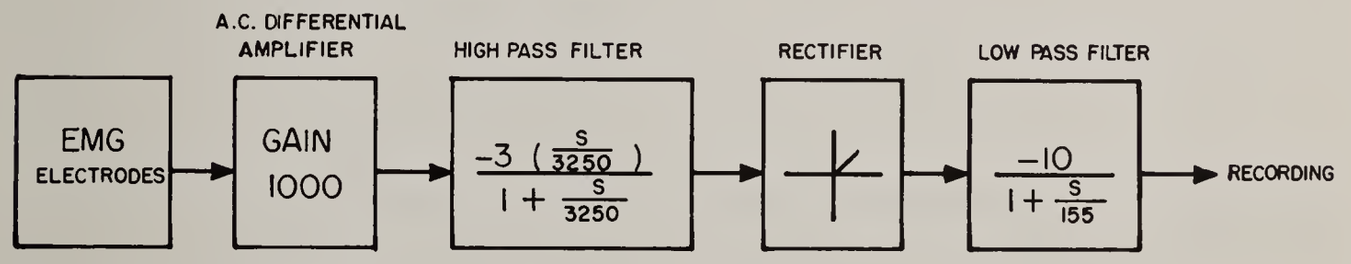

Fig. 2.—EMG Processing Circuit.

pick-ups were amplified using a.c. differential amplifiers. In some experiments, the amplified EMG activity was processed by a high pass filter, a rectifier, and a low pass filter units as shown in Figure 2.

The IBM 1800 computer was used for on-line editing and storage of five channel data on the magnetic tape: hammer force, foot plate torque, foot plate angle, emg of anterior tibial muscle, and emg of gastrocnemius muscle. A special thresh-

old program monitored the hammer output continuously during the course of the experiment and whenever a pre-set threshold level was reached, the control was transferred to a data storage program which stored data for 200 msec before and 800 msec after the threshold point at a sampling rate of 1000 per sec. The initial foot torque was measured at 100 msec before the hammer pulse input. This program allowed hammer inputs at random intervals to exclude any possibility of the subject's anticipation and also provided for automatic data storage capability. Slowed reruns of the tests made plotting on an X-Y recorder possible. The computer data processing was done off-line. Similar responses were obtained in the three normal subjects tested. Most of the data reported here is of one subject (GA) for a more precise comparison between different conditions.

IV. Results

(a) Isometric Contraction

In the isometric condition, the foot plate is fixed in an anatomical position such that the sole of the foot is at approximately a right angle with respect to the lower leg. The subject is instructed to maintain some constant force in plantarflexion or dorsiflexion direction against the foot plate.

In Figure 3, the hammer force, foot torque, and EMG activities of the anterior tibial and gastrocnemius-soleus muscles are shown for a typical response. It is interesting to note that the anterior

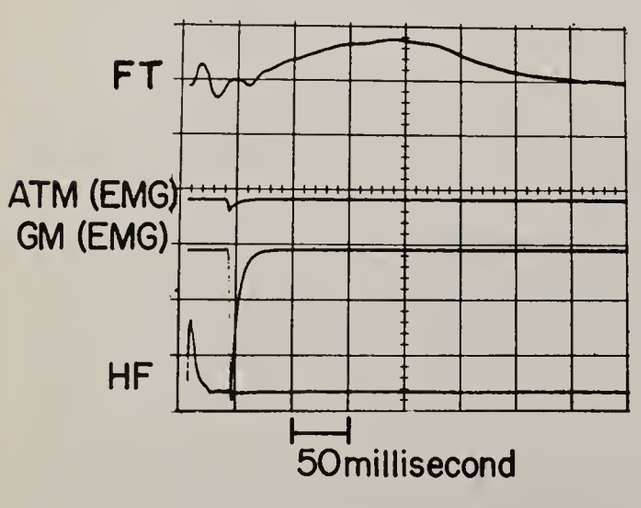

Fig. 3.—A Typical Tendon Jerk Response in Isometric Condition.

tibial muscle, which is an antagonist, has EMG activity synchronous to the EMG activity in gastrocnemius-soleus muscle. The latency of the EMG activity is about 40 msec from the point of onset of the hammer tap.

In Figure 4, several foot torque response for different magnitudes of both the hammer force and the initial foot torque (voluntary contraction) are shown. The shape of the response curves remain unchanged for various magnitudes of these variables. However, the time, at which the maximum foot torque response is obtained, occurs earlier as the initial foot torque is increased in the plantarflexion direction.

The data analysis is carried out considering the hammer force (HF) and the initial foot torque (IFT) as the independent or the control variables. The dependent or the response variables are (a) the magnitude of maximum change in foot torque in the reflex response with respect to the initial foot torque, this variable will henceforth be called delta foot torque (ΔFT); and (b) the time delay at which this maximum foot torque occurs with respect to the hammer force input, this variable will be denoted by Tm. Due to an initial hammer blow artifact in the foot torque response, detection of the onset of the response was difficult to program on the computer and consequently this variable, which is roughly equal to 50 msec, was not used for analysis.

The dependence of delta foot torque (ΔFT) on hammer force is portrayed in Figure 5. These data clearly suggest a strong functional relationship between ΔFT and HF. The maximum value of ΔFT (0.4 Kg.m.) is about one-half of the maximum voluntary IFT (0.8 Kg.m.) used in this experiment. The maximum value of ΔFT is, however, very small (about 2%) compared to the maximum isometric foot torque that the calf muscles are capable of producing (see discussion). ΔFT decreases slightly for HF$>$ 1.2 Kg. The initial threshold (dead space) to elicit any measurable ΔFT response is about 0.125 Kg which is approximately 7% of input domain of HF.

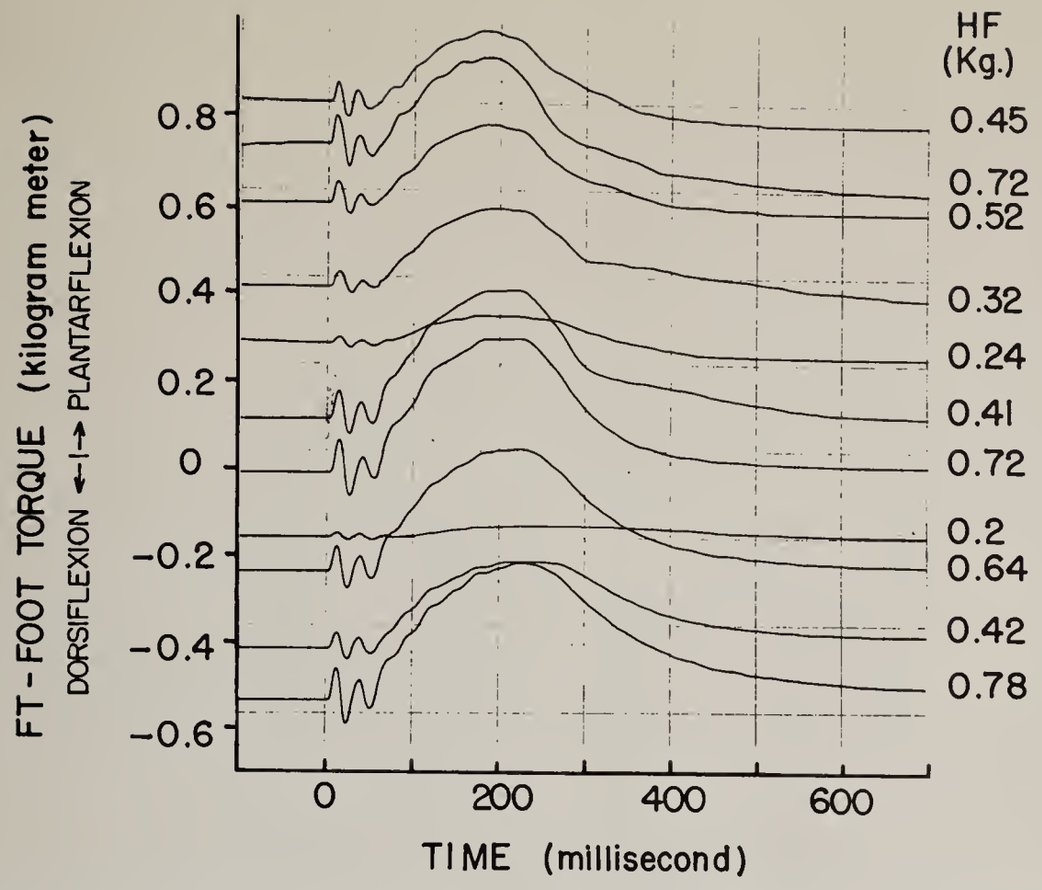

Fig. 4.—Foot Torque (FT) Response for various magnitudes of Hammer Force (HF) and Initial Foot Torque (IFT).

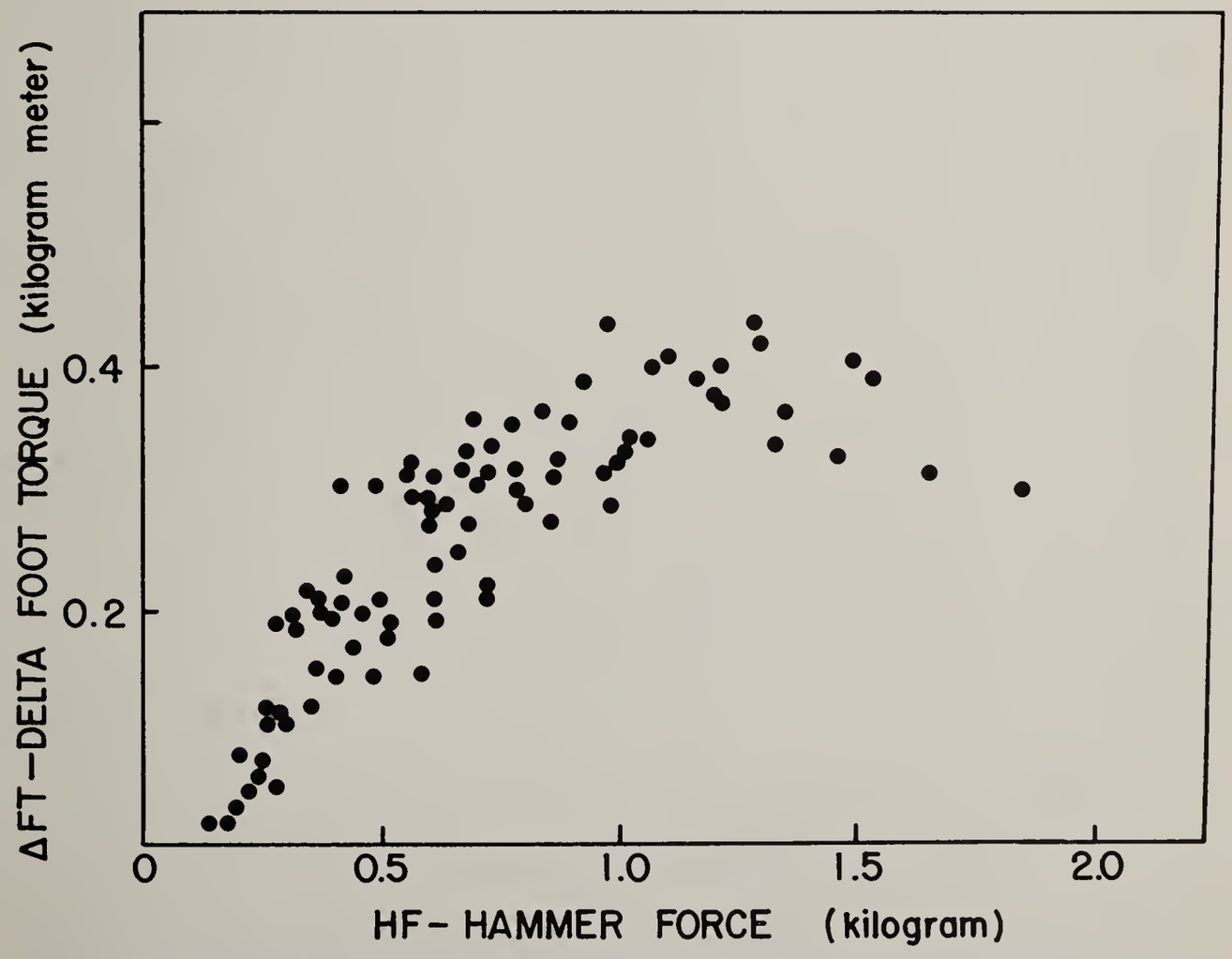

Fig. 5.—Delta Foot Torque (ΔFT) versus Hammer Force (HF), 0.5 Kg.m (dorsiflexion) $\leq$ IFT $\leq$ 0.8 Kg.m. (plantarflexion).

In figure 6, FT is plotted against IFT (plantarflexion torque considered positive) with HF as parameter. This data is taken for $0.5 < HF < 1.0$ Kg. Only modest deviation from a constant function is seen with some fall off at high IFT. The IFT for ΔFT vs HF data in Figure 5 range from 0.6 Kg.m. dorsiflexion to 0.8 Kg.m. plantarflexion. Small variance in the data, well within the physiological variabilities, suggests additionally that the dependence of ΔFT on IFT is weak as compared to a strong dependence of ΔFT on HF.

The time (Tm) at which the maximum torque occurs is plotted against hammer force in Figure 7. This widely scattered data do not suggest any meaningful relation between Tm and HF. In Figure 8, Tm is plotted versus initial foot torque (IFT). For IFT in the plantarflexion direction there is a short latency of about 180 msec whereas for IFT in dorsiflexion direction the latency is about 220 msec.

In Figure 9, the dependent variable Tm is plotted against the other dependent variable ΔFT. This data is for $0.125 < HF < 1.875$ Kg. and $-0.6 < IFT < 0.8$ Kg.m. This plot also does not indicate any meaningful correlation between Tm and ΔFT.

(b) Isotonic Contraction

In the isotonic condition, two different experiments were performed. In the first experiment, the subject was instructed to voluntarily assume various initial foot angles while the foot plate was free to rotate without externally applied torque. In the second experiment, the subject was instructed to remain completely relaxed (as far as possible) while the initial foot angle was changed by applying various external torques.

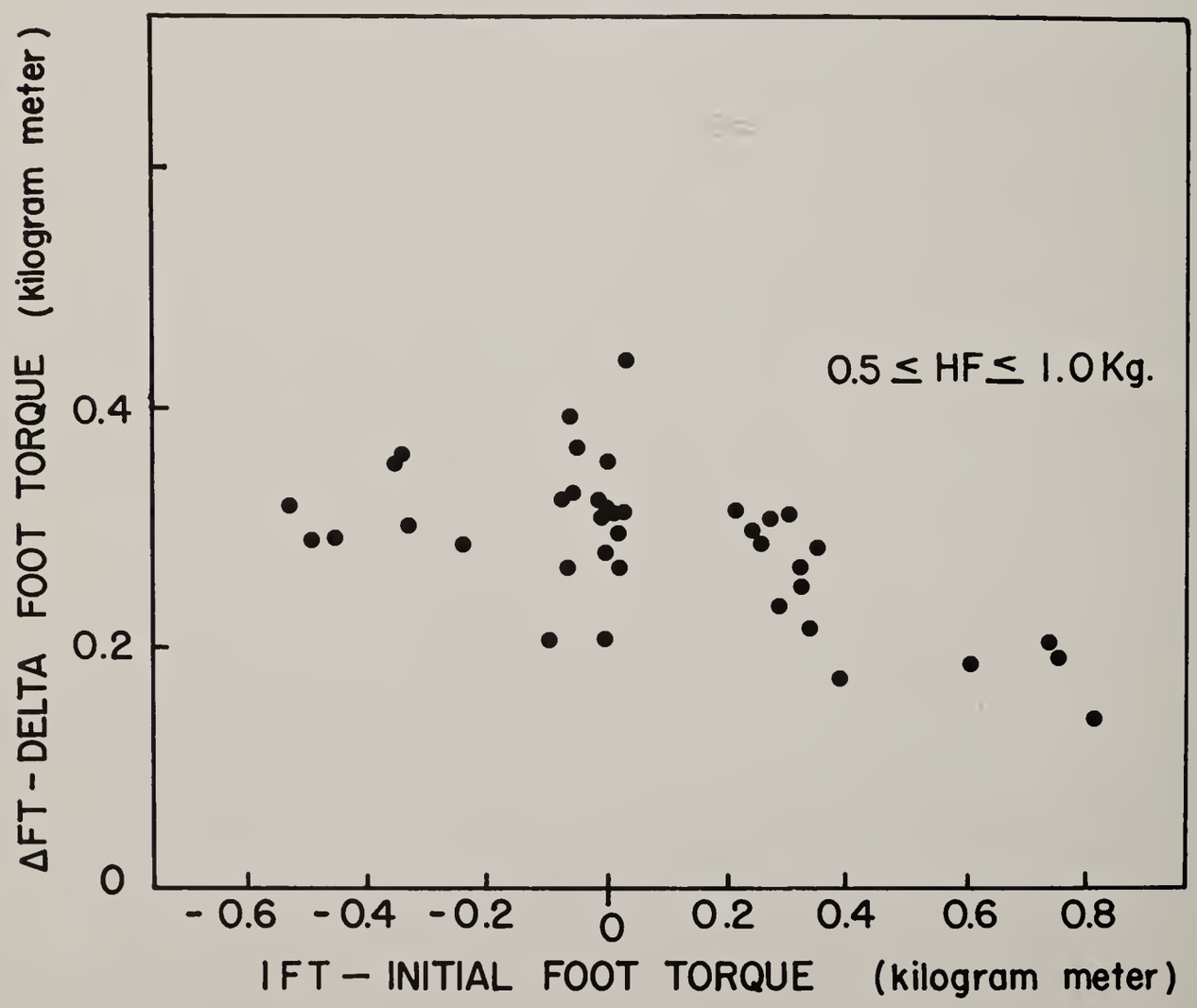

Fig. 6.—Delta Foot Torque (ΔFT) versus Initial Foot Torque (IFT), $0.5 \leq HF \leq 1$ Kg.

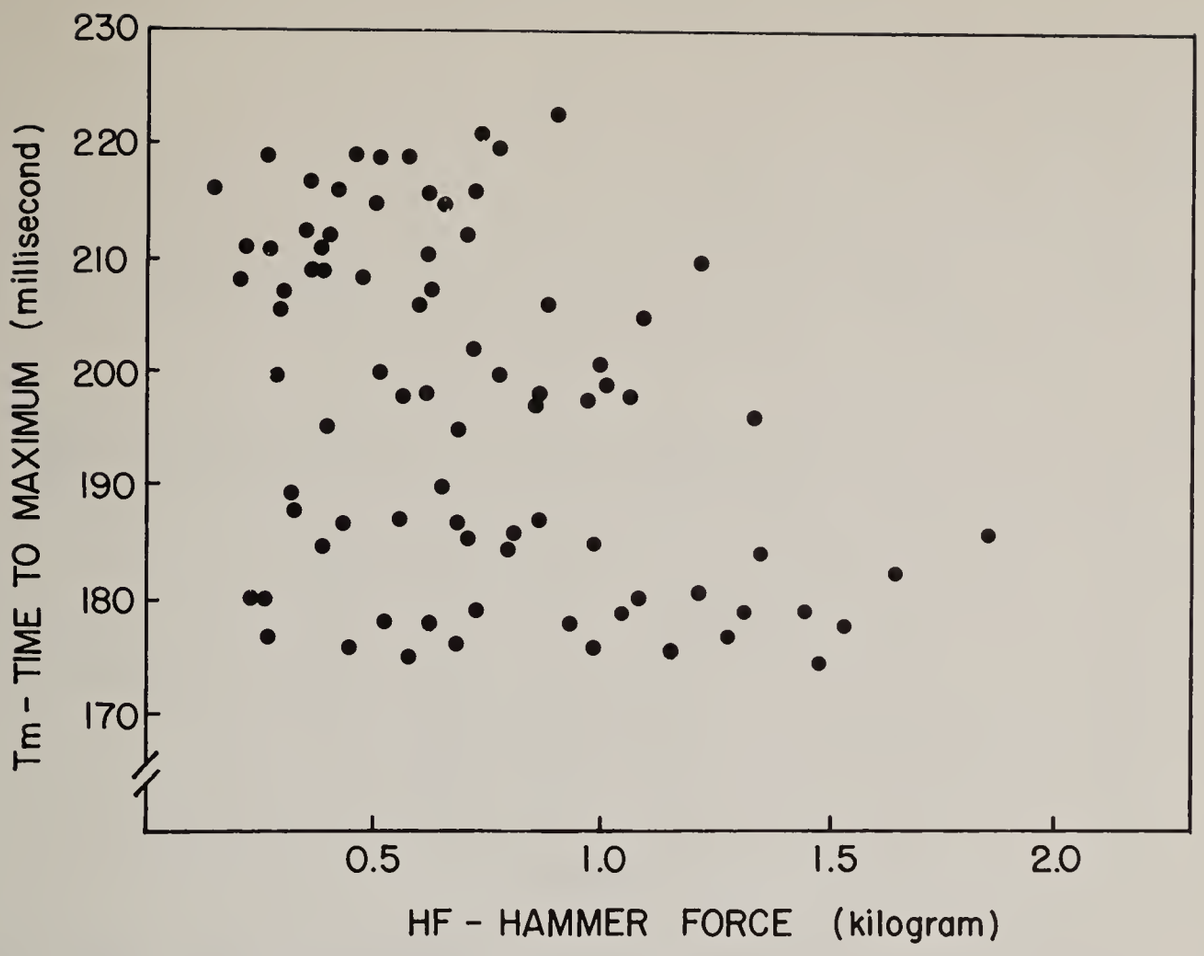

Fig. 7.—Time at which the Maximum Foot Torque Response occurs (Tm) versus Hammer Force (HF).

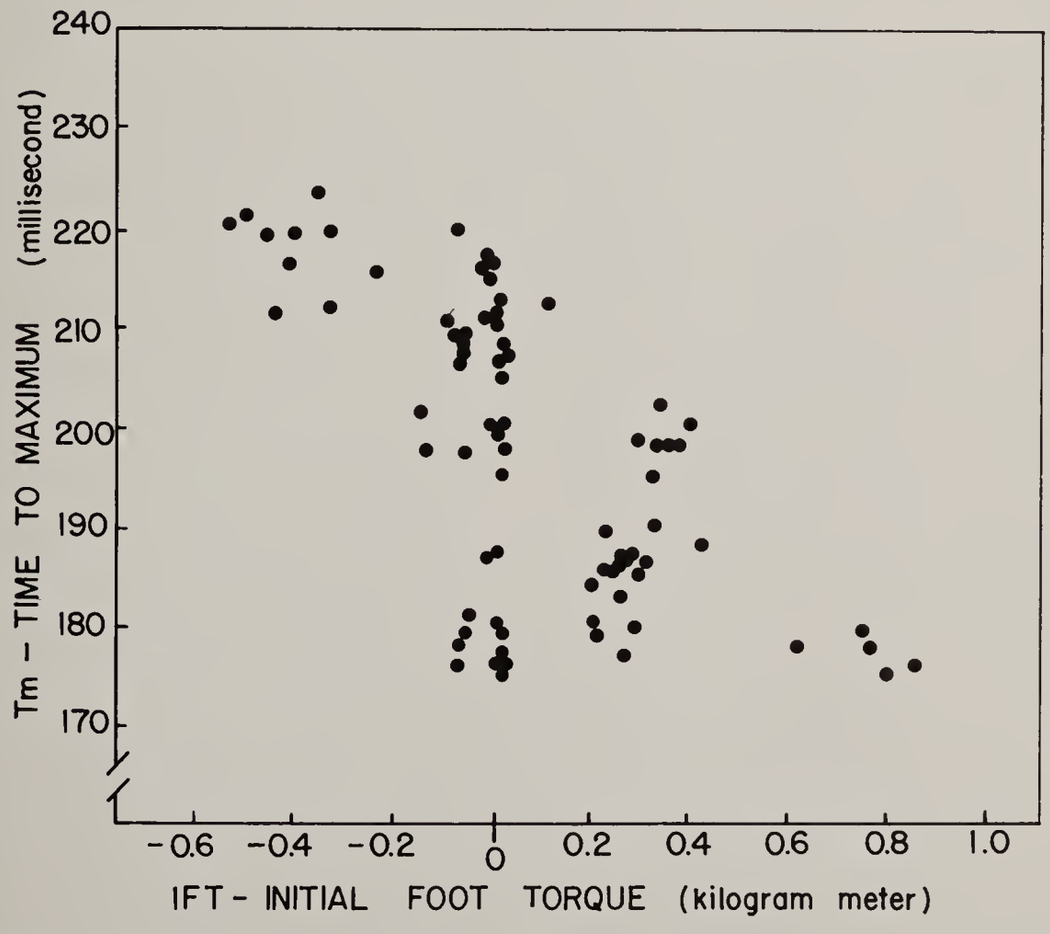

Fig. 8.—Tm versus Initial Foot Torque (IFT).

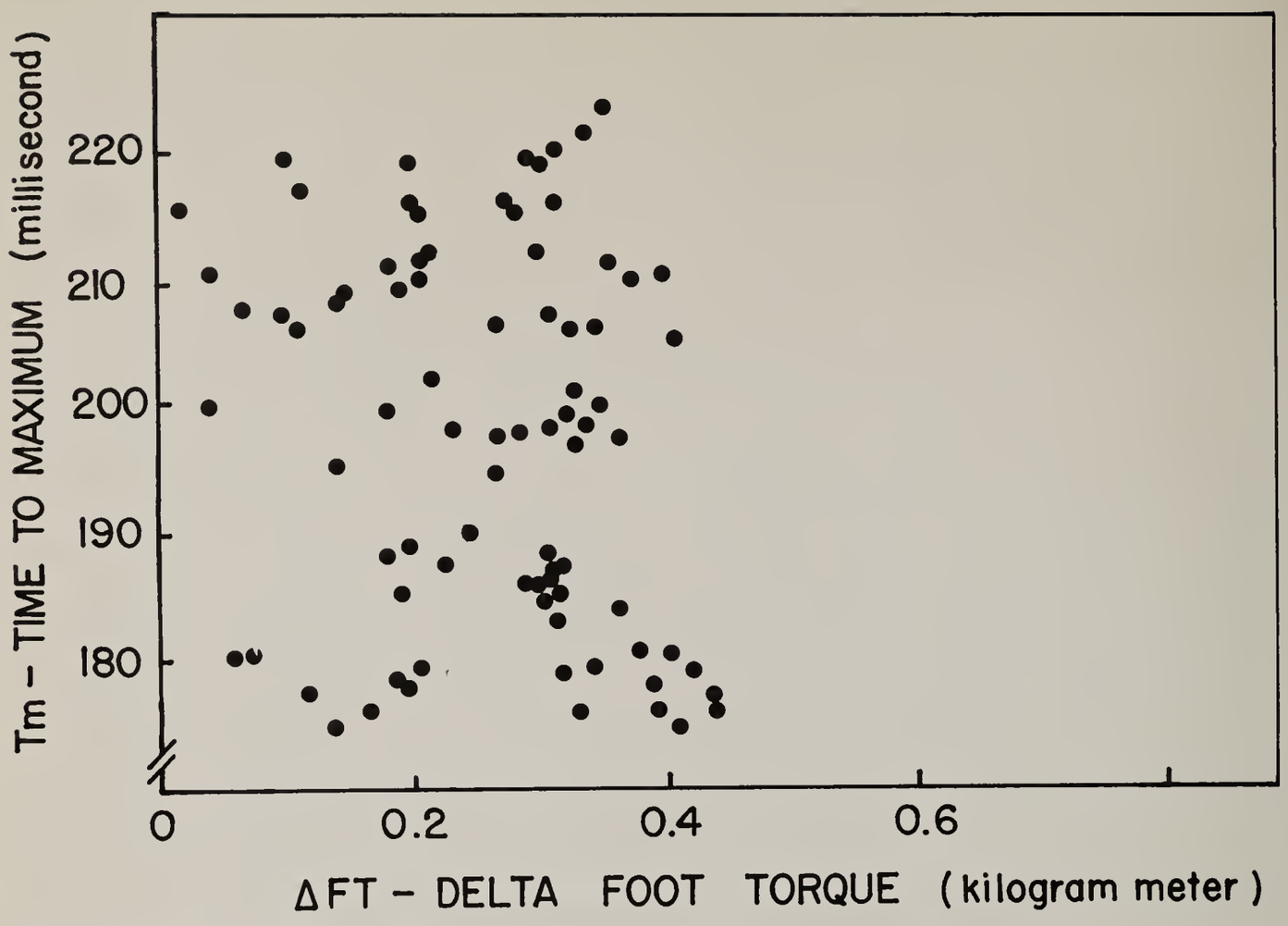

Fig. 9.—Tm versus Delta Foot Torque (ΔFT).

Isotonic—Case I

In Figure 10, the hammer force, foot angle, and EMG activities of the anterior tibial and gastrocnemius muscles are shown for a typical response.

In Figure 11 (response a), the foot plate is at about 90° with respect to the lower leg. In this case, the response starts with a latency of about 60 msec, reaches a maximum value at about 150 msec and remains relatively constant at this maximum value for about 120 msec, and finally returns to the resting position at about 440 msec. In response b, when the foot is in voluntary dorsiflexion, the onset of response is at 60 msec, reaches maximum at 270 msec and remains at the maximum response for 75 msec and returns to the original position at 650 msec. In response c, when the foot is in voluntary plantarflexion, the maximum is reached at 130 msec, remains at the maximum value for 80 msec and returns to the base line at 350 msec. The inertia of the foot plate is negligibly small compared to the inertia of the foot and therefore it is safe to assume that the external resistive force is zero.

Unlike the foot torque response in the isometric case, the form of the foot angle response in the isotonic case depends considerably on the initial voluntary foot angle, or in other words the initial muscle length. The control variables in this case are the hammer force (HF) and the initial foot angle (IFA). One of the response variables is the magnitude of maximum foot angle in the reflex response with respect to the initial foot angle, this variable will henceforth be called delta foot angle (ΔFA). The second response variable is the time at which the maximum foot angle response occurs, this variable will be denoted by Tm.

The variability of the foot angle response poses some difficulties in the computer analysis of a large number of

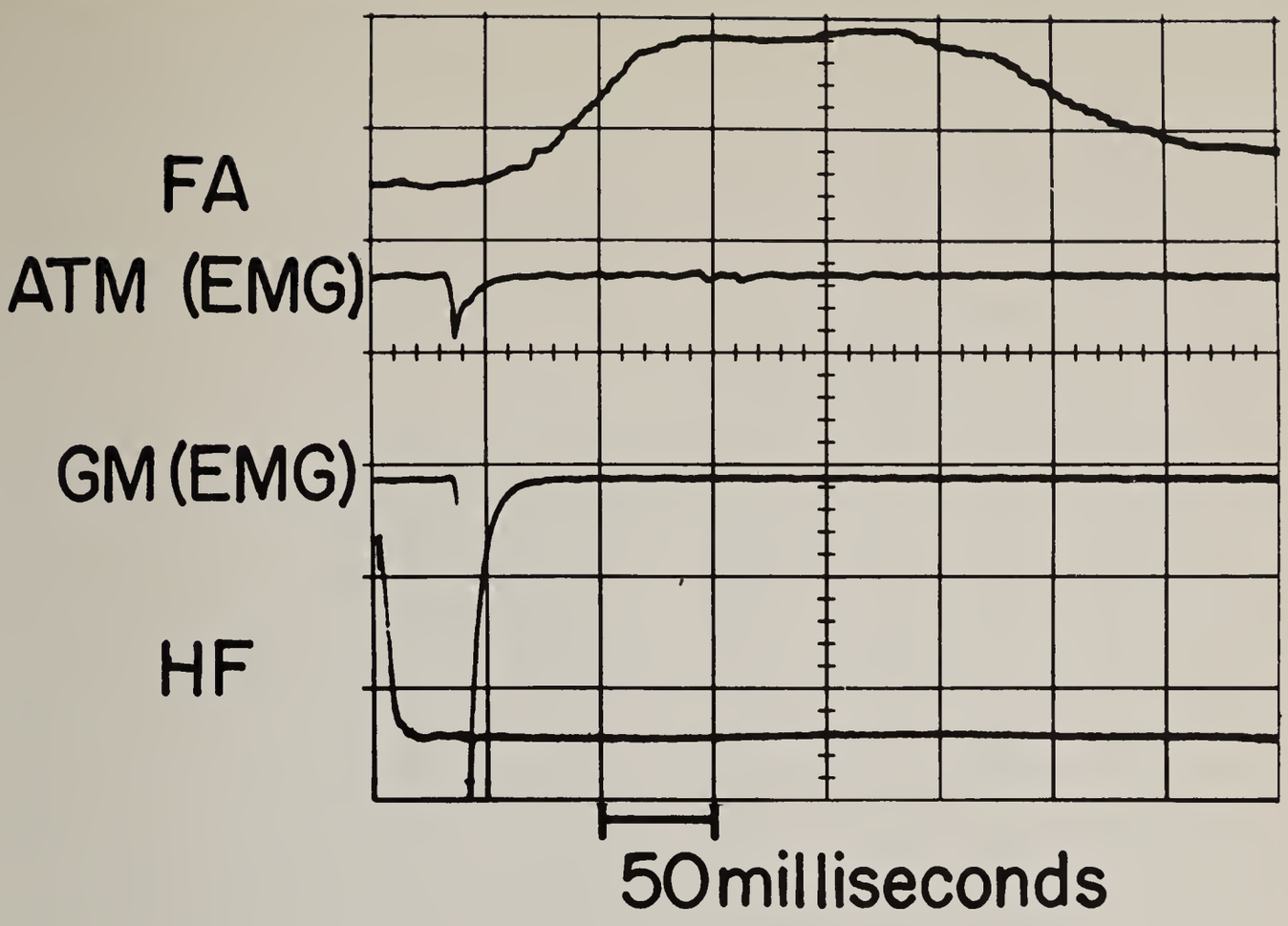

Fig. 10.—A Typical Tendon Jerk Response in Isotonic Condition, no external loading.

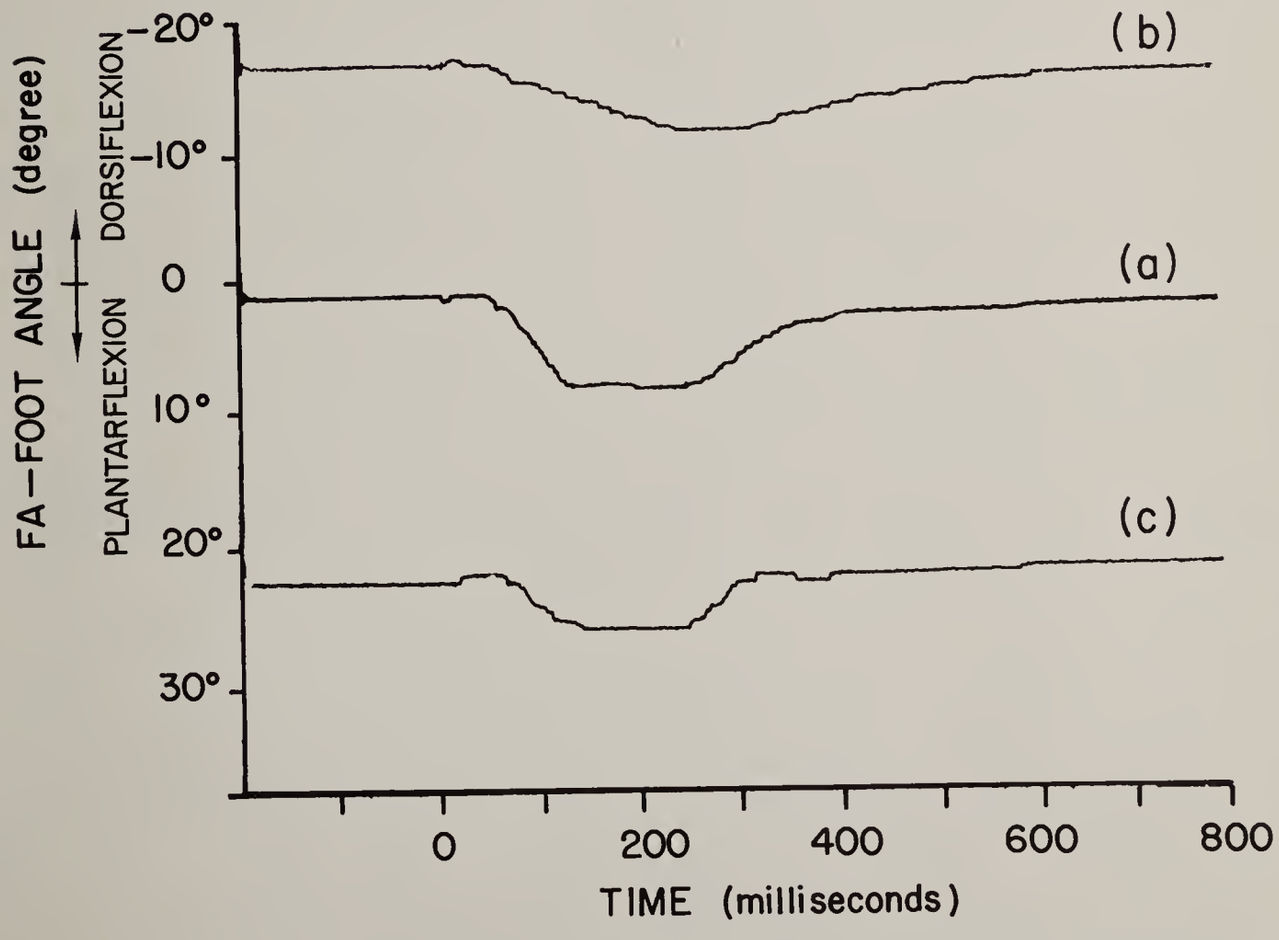

Fig. 11.—Foot Angle Response for various values of Hammer Force (HF) and Voluntary Initial Foot Angle (IFA), no external loading.

foot angle response for ΔFA and Tm. The time at which the maximum ΔFA occurs is not a well defined point. In most responses there is a *plateau* of duration from about 75 to 120 msec after the initial movement and before the second corrective type response. A small noise signal due to 60 cps pickup and other sources will cause very little error in the magnitude of FA but may introduce considerable error in defining Tm. Consequently, the variance in Tm is fairly large.

In Figure 12, ΔFA is plotted against HF. Here again we notice a strong functional relationship between ΔFA and HF over the range of $0 \leq \Delta FA \leq 8.5°$ for 5° (dorsiflexion) $\leq$ IFA $\leq$ 10° (plantarflexion). The extreme voluntary range for IFA is from about 30° dorsiflexion to about 60° plantarflexion. There is a dead band of about 0.325 Kg which is about 16% of input domain of HF as compared to 7% in isometric case. In Figure 13, ΔFA is plotted against voluntary IFA. This data seems to be inadequate to predict any definite relationship between ΔFA and voluntary IFA. In Figure 14, Tm is plotted against voluntary IFA. The minimum value of Tm is 145 msec in plantarflexion whereas the maximum value is 340 msec in dorsiflexion.

Isotonic—Case II

While the subject was relaxed, an involuntary initial foot angle was imposed on the foot by means of an externally applied torque to the foot plate. A relatively long spring attached to the foot plate provides a nearly constant force (torque on the foot plate) for small deflections of the foot plate, the torque variation in tendon jerk responses amounted to less than 20% of the steady state value. The initial involuntary foot angle was varied by changing the external

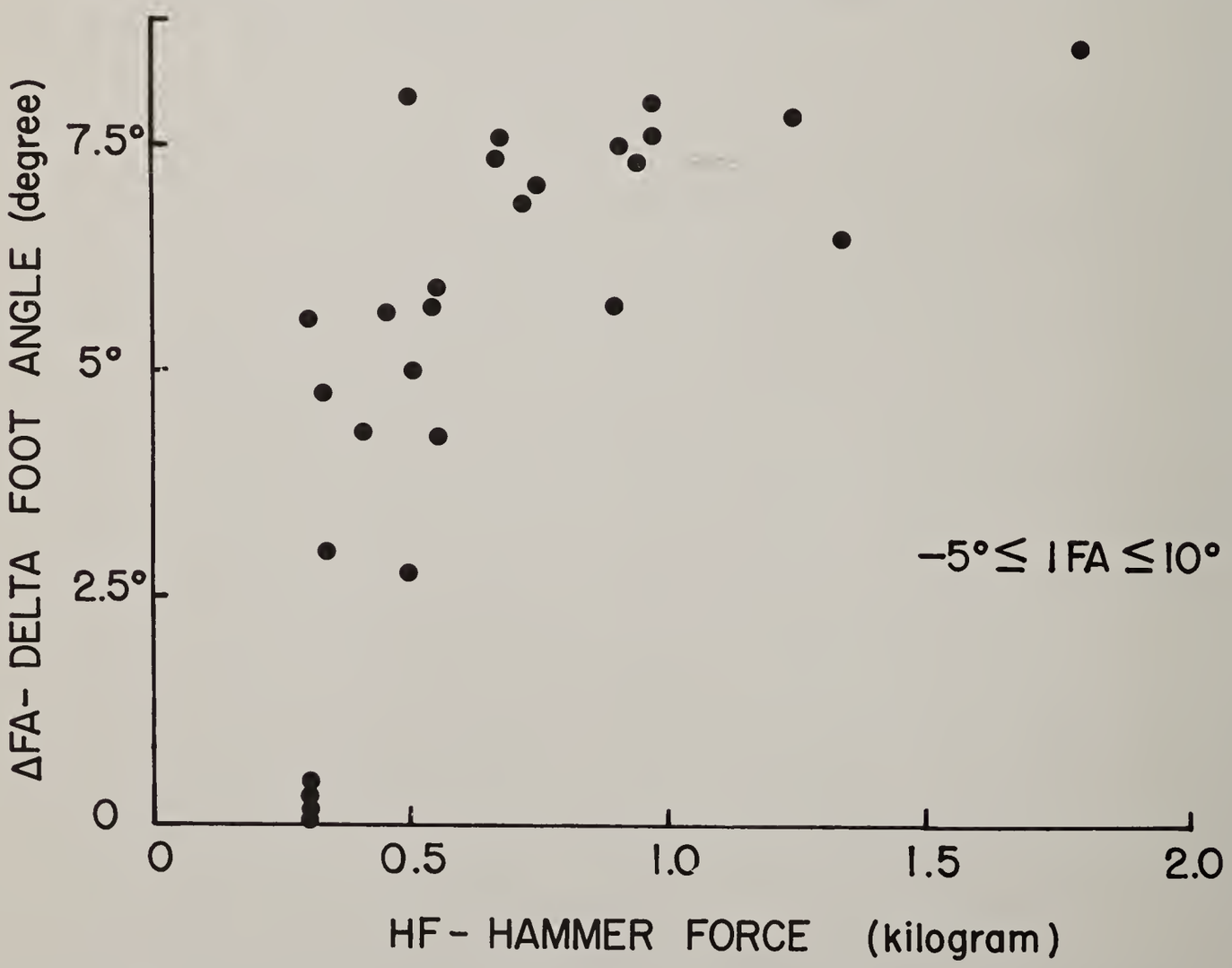

Fig. 12.—Delta Foot Angle (ΔFA) versus Hammer Force (HF), 5° (dorsiflexion) $\leq$ IFA $\leq$ 10° (plantarflexion), no external loading.

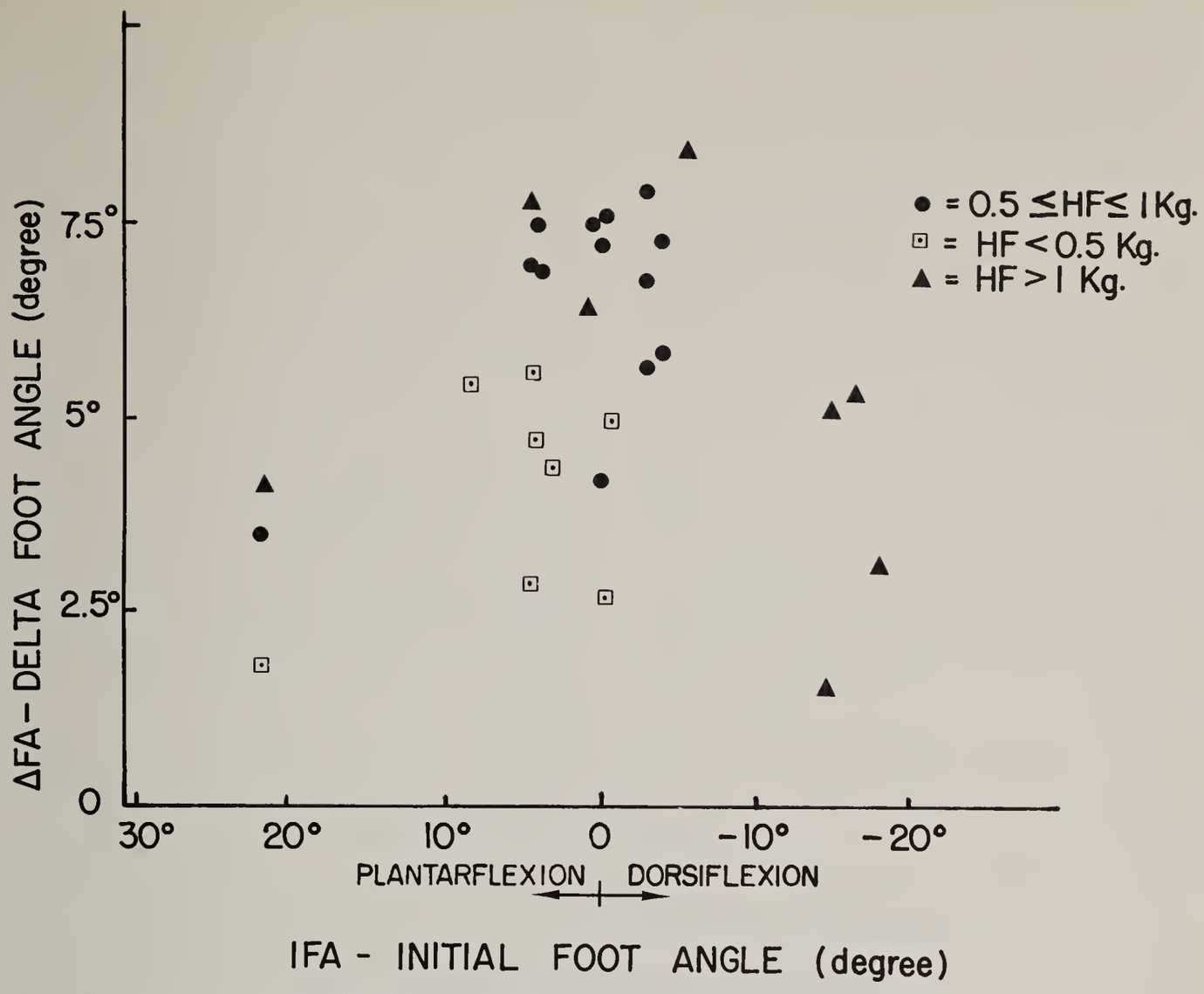

Fig. 13.—Delta Foot Angle (ΔFA) versus voluntary Initial Foot Angle (IFA).

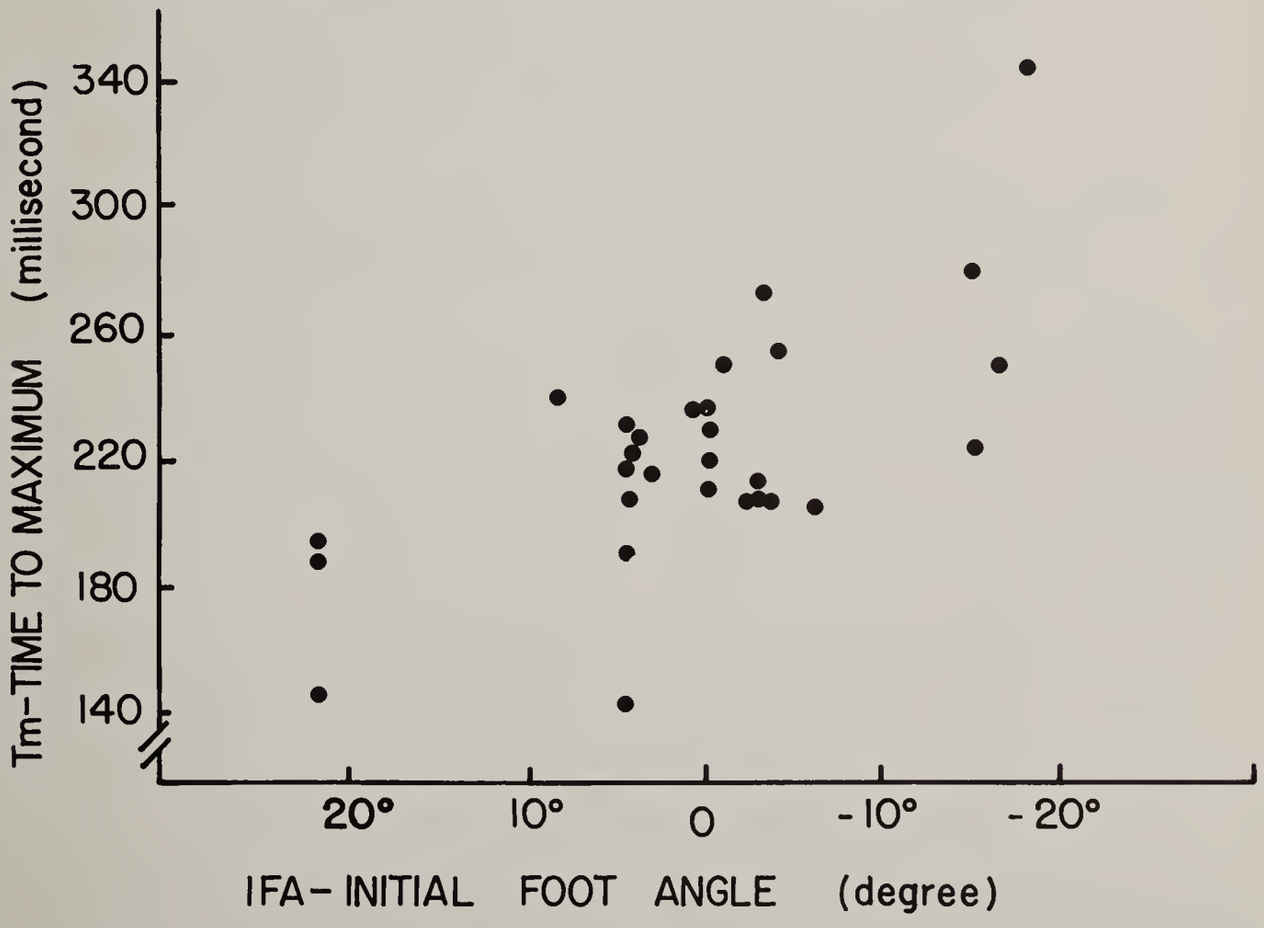

Fig. 14.—Time at which the Maximum Foot Angle Response occurs (Tm) versus voluntary Initial Foot Angle (IFA), no external loading.

torque (ET), that is, by changing the spring tension.

As the initial involuntary foot angle is varied from extreme dorsiflexion to extreme plantarflexion, the amplitude of the foot angle response decreases. In Figure 15, the foot angle response for various initial involuntary foot angles is shown as function of time. For each of these responses, the hammer force was saturating, that is, it was sufficient to produce a maximal foot angle deflection. The relationship between delta foot angle (ΔFA) and involuntary initial foot angle (IFA) for a saturating hammer force is shown in Figure 16. Note that for initial foot angles of greater than 15° in the plantar direction, ΔFA is essentially equal to zero. The small nonzero values for ΔFA is due to the initial artifact of angular deflection produced by the hammer blow (see last response in Figure 15).

In general, there is a sigmoid relationship between hammer force (HF) and delta foot angle (ΔFA); that is, there is a saturation and initial threshold (dead band). The shape of this sigmoid relationship, however, is a function of the initial involuntary foot angle due to external torque (ET). ΔFT as a function of HF for various initial foot angles is shown in Figure 17. As indicated above, the maximum response in Figure 17 is observed to decrease as the IFA becomes more plantar. The values of ΔFA below 1° can be attributed to the hammer blow

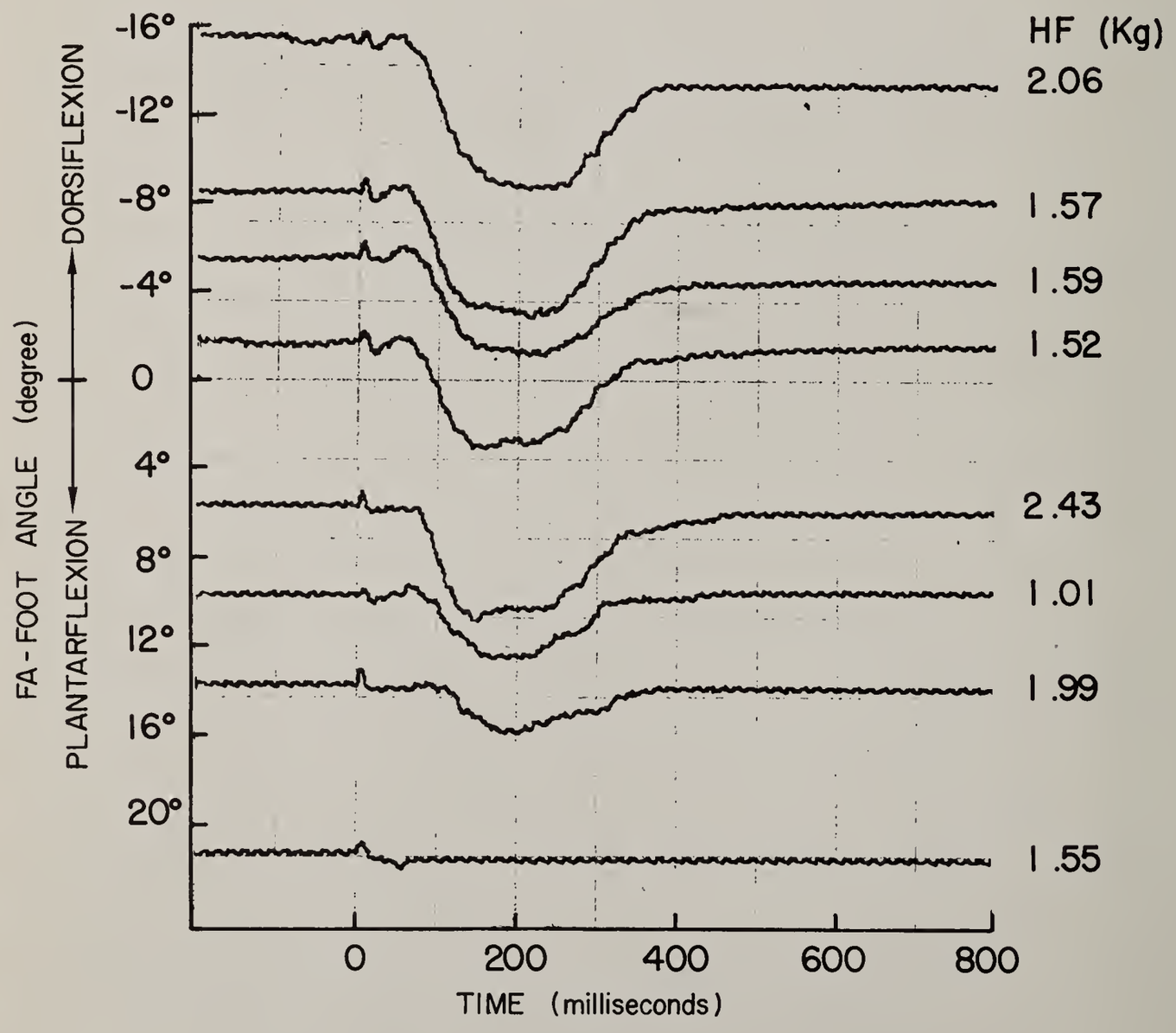

Fig. 15.—Foot Angle Response for various values of Involuntary Initial Foot Angle (IFA) due to External Torque (ET) and saturating Hammer Force (HF).

artifact and 60 Hz noise signal. Therefore, from Figure 17, the threshold (dead band) to hammer force stimulation increases as the initial foot angle becomes more plantar.

Not only does the amplitude of ΔFA change under different conditions of external loading, but the shape of the foot angle response curve changes as well. The typical responses shown in Figure 15 indicate that under conditions of extreme plantarflexion the onset of the deflection is increased while the total duration of the deflection is decreased. Under conditions of moderate to extreme dorsal or plantar flexion the plateau becomes less distinct.

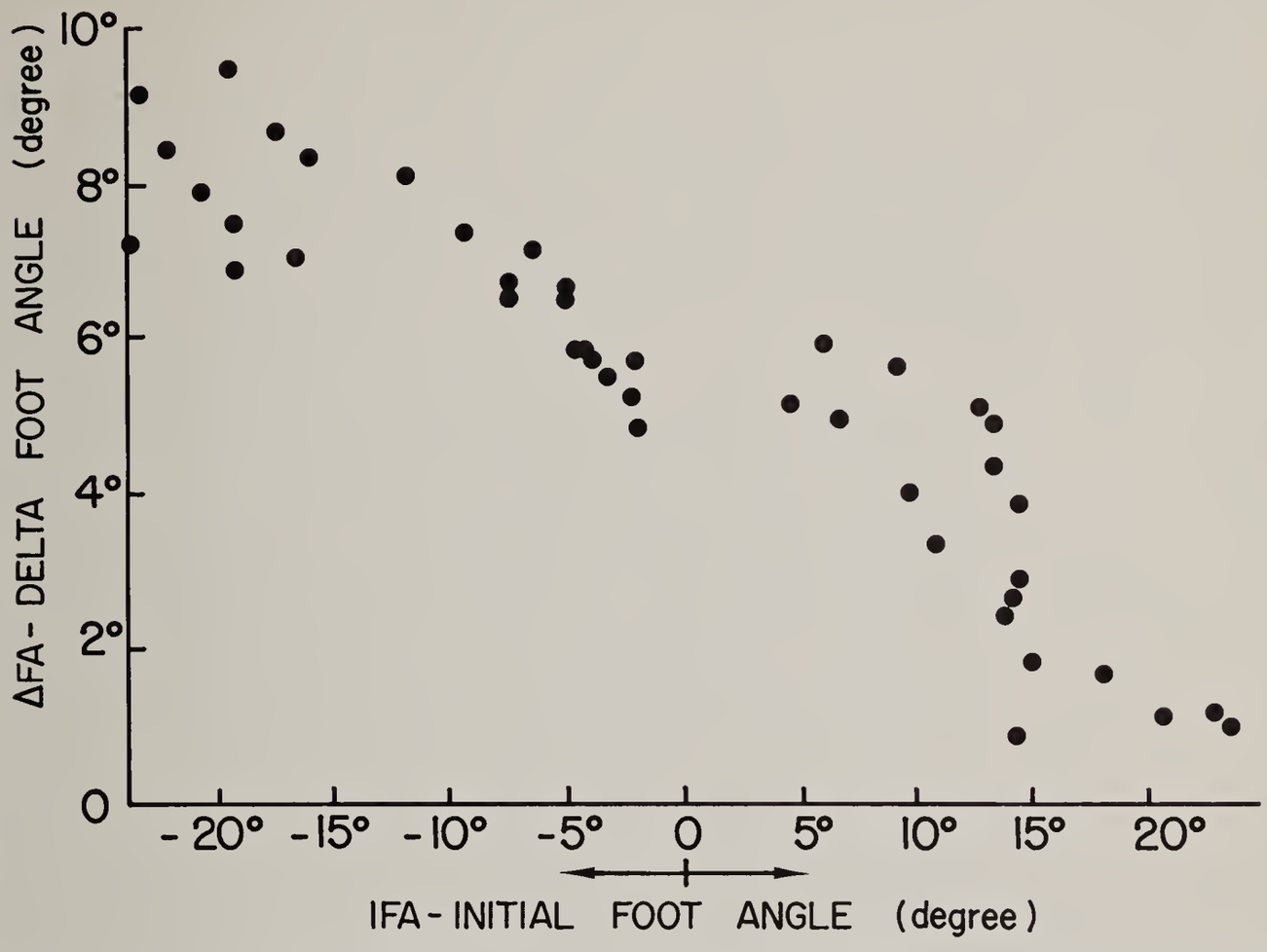

Fig. 16.—Delta Foot Angle (ΔFA) versus Involuntary Initial Foot Angle (IFA) due to External Torque (ET).

V. Discussion

(a) Isometric Condition

EMG Activity

The gastrocnemius muscle is stretched due to the percussion at the tendon. Simultaneously, the anterior tibial muscle is also stretched due to slight movement of the foot and the foot plate resulting from the hammer blow. Therefore, it seems that the hammer blow at achilles tendon stretches both the gastrocnemius-soleus and the anterior tibial muscle nearly simultaneously. This clearly explains the simultaneous EMG activities in the ATM and GM as shown in Figure 3 which start with a latency of about 40 msec after the hammer impact. The tendon jerk response, therefore, is not due to the gastrocnemius-soleus muscle alone but is the net response of the gastrocnemius-soleus and anterior tibial muscle acting against each other.

In experiments on decerebrate M. supraspinatus in cats it has been found that a very small stretch stimuli (taps)

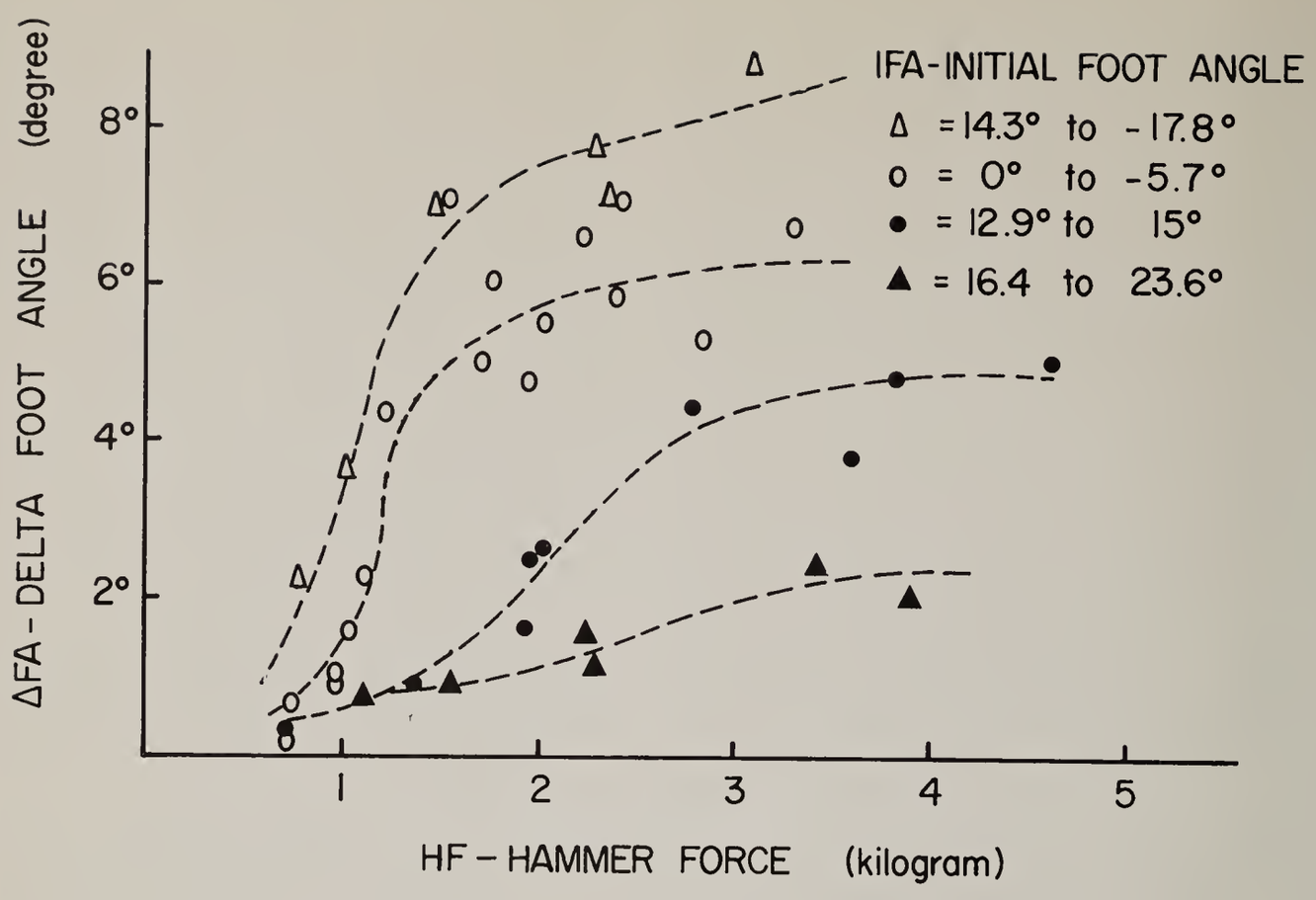

Fig. 17.—Delta Foot Angle (ΔFA) versus Hammer Force (HF) for various values of Involuntary Initial Foot Angle (IFA) due to External Torque (ET).

can elicit a well-marked response. A stretch of 8 μ[circa 0.02%] of the tendon is sufficient to elicit a response developing 0.32kg of tension in this muscle, whose longest fasciculi average some 50 or 70 mm and whose shortest some 26mm [22.]

Latency

The 40 msec time delay in the EMG comprises of the conduction time to and from the spinal cord, conduction time within the cord itself and the central delay. In the experiments done by Magladery et al [23] on human subjects, the latency of the H-wave in the calf muscle for an electrical stimulus to posterior tibial nerve in popliteal fossa is about 32 msec. The H-wave, as output, corresponds to the mechanically provoked EMG by percussion of the tendon, although the input path is of course more direct [24]. Lambert et al [10] have reported a time delay of about 35 msec from start of tap to start of muscle action potential.

The time delay in the foot torque response is about 50 msec (Fig. 4). This additional 10 msec delay is the time required to develop a measurable force from the moment the efferent volleys reach the muscle. Chaney [9] has also reported a time delay of about 50 msec between the tendon-jerk stimulus and the beginning of the tension response. The time of onset of the response seems to be independent of the initial foot torque as well as the hammer force.

ΔFT versus HF

There was no observable response for hammer force less than 0.125kg which, therefore, represents an initial threshold of approximately 7% of the input domain of HF (Figure 5). ΔFT initially increases with increased hammer force and attains a peak value of about 0.4 kg.m. at about 1.125 kg HF. For HF greater than 1.125

kg foot torque response decreases. The maximum voluntary initial foot torque used in this experiment is 0.8 kg.m. Lippold [33] measured the maximum tension that could be exerted by the calf muscles of different subjects, ranging from about 30 kg to 100 kg with a lever arm of about a foot, that is, the maximum isometric torque ranges from 10 kg.m. to 30 kg.m. The maximum ΔFT of 0.4 kg.m. in these experiments is only about 2% of the maximum isometric torque that the gastrocnemius-soleus muscles are capable of producing.

Granit [27] has shown that for the soleus stretch reflexes in cats the reflex tension developed in the muscle is proportional to the amount of stretch (muscle extension). In the present experiments on normal human subjects any direct measurement of the muscle extension is difficult for both ethical and experimental reasons. The muscle extension or stretch is some nonlinear function of the initial foot torque and the hammer force. The nature of this relationship has not yet been studied. The nonlinear nature of ΔFT versus HF curve (Figure 5) could very well be in part due to the nonlinear nature of the muscle extension as a function of IFT and HF.

ΔFT versus IFT

The relationship of ΔFT as a function of IFT with HF as a parameter is shown in Figure 6. The range of HF is from 0.5 kg to 1.0 kg. When IFT is in the dorsiflexion direction, the gastrocnemius-soleus muscle is relatively inactive prior to the hammer input, consequently the ΔFT response is independent of IFT. For IFT in the plantarflexion direction, ΔFT decreases somewhat as IFT increases. There may be several possible contributing factors for this inhibition when IFT is in the plantarflexion.

The mechanical factor which is in part responsible for this decreased response is a decrease in the spindle receptor stretch when IFT increases. The initial tension in the gastrocnemius-soleus muscle is proportional to IFT (plantarflexion). As the tension in the gastrocnemius-soleus increases the amount of stretch of the muscle for the same hammer input decreases and therefore, the amount of stretch of the spindle receptor decreases. This does not necessarily mean that the afferent signal decreases. The output of the spindle at the same time depends on the gamma inputs and the relative sensitivity of the spindle as a function of the muscle tension.

Another possible explanation of this inhibition comes from the observations by Granit in cat's gastrocnemius muscle [28]. Granit observed that the muscle tension is the most important factor in determining the form of the excitability curve of the motoneurons under proprioceptive firing. He concluded that the increase of initial tension, within limits, may augment the excitatory phase of the excitability curve but has fairly regular and relatively greater effect on the inhibitory trough which deepens and expands. In recent studies [29-31] it has been shown that this inhibition is due in part to autogenetic inhibitory afferent impulses from the golgi tendon organs.

Tm—Time to Maximum

The time at which the maximum foot torque response with respect to the initial foot torque occurs, shows a dependence on IFT being less when the initial foot is in the plantarflexion than when the initial foot torque is in dorsiflexion. The range of Tm for the data shown in Figure 7 and 8 is from 175 msec to 223 msec with an average value of about 198 msec and standard deviation of 14.8 msec. The data shows a wide variance in the value of Tm within a narrow band about zero foot torque position bridging between a long latency when IFT is in the dorsiflexion direction and a short latency for the plantarflexion direction. The average value from the start of tap to the peak of contraction in normal subjects in the experiments done by Lambert et al [11] is 186 msec. Levy [25] has shown that during a reflex contraction of the calf muscle, the soleus muscle

is taking a greater part in this contraction than the gastrocnemius muscle. The gastrocnemius is a fast muscle, having a contraction time in the range of 25-40 msec in cats, whereas, the soleus is a slow muscle with a contraction time in the range of 94-120 msec in cats [25, page 127]. Our data in man indicate an average contraction time of about 158 msec from the start of EMG to maximum foot torque. Lambert et al [11] have reported the average contraction time in normal man of 150 msec from start of potential to peak of contraction.

The nature of the Tm versus IFT relation may be explained in part by considering the stiffness of the muscle and its relation to the spindle output. When the muscle is tense, as the gastrocnemius is in the case of plantarflexion IFT, a tendon jerk will cause more synchronous output from the spindle as compared to when the muscle is slack. This synchronous afferent signal will generate a synchronous efferent signal which is propagated on α-fibers, consequently the tension will increase more rapidly. The role of the gamma input and its possible relationship with IFT must also be considered. Also, when the muscle tension is increased, a small change in muscle length due to a hammer blow will be transmitted to the spindle (i.e., change in spindle length) in a relatively shorter time. This time delay, from the moment the hammer strikes the tendon to the time the spindle firing rate increases, is possibly only of the order of a few msec and consequently, it will contribute only a small amount to this overall spread of about 40 msec. There may possibly be some contribution from the viscoelastic forces in the muscle tending to increase the delay time when the muscle is slack. Figure 7 (Tm versus HF) and Figure 9 (Tm versus ΔFT) do not suggest any meaningful correlation between these corresponding variables. The Tm versus IFT relation in Figure 8 could possibly be approximated by three piecewise linear portions where the center portion passing through the zero torque position has larger slope.

(b) Isotonic Condition

Case I—No External Torque

In the isotonic response (Figure 10) the EMG activity in the anterior tibial muscle is again due to a small initial stretch of this muscle because of the hammer blow at achilles tendon. The foot angle response, therefore, is the net response of these antagonist muscles (gastrocnemius and anterior tibial).

The plateau in our isotonic responses varies from about 75 to 120 msec. It is interesting to note that this plateau is maximum when the foot plate is at about 90° with respect to the lower leg and the duration decreases both for dorsiflexion and for plantarflexion initial foot angles. The possible origin of this plateau is discussed later on in Case II.

In Figure 12, ΔFA is plotted against HF for 5° (dorsiflexion) to 10° (plantarflexion) voluntary IFA. There is a strong functional relationship between ΔFA and HF over the range of $0 \leq \Delta FA \leq 8.5°$ for $0.325 \leq HF \leq 2$ Kg. The initial dead band (or threshold) is about 0.325 kg HF as compared to 0.125 kg HF in the isometric case or 16% of the input domain as compared to 7% in isometric case. The ΔFA response is a saturation type function without fall off at large HF [see Figure 5]. In Figure 13, ΔFA is plotted as a function of voluntary IFA for various ranges of HF. The data is clearly inadequate to define any meaningful correlation between ΔFA and voluntary IFA. The isotonic responses are much more complicated than the isometric responses and therefore large amounts of data and careful analysis is warranted.

In Figure 14, the time at which the initial maximum foot angle response (i.e., the onset of the plateau) Tm is plotted against voluntary IFA. There is a considerable variation in the data but it is consistent with the isometric experiment. In dorsiflexion the maximum value of Tm is about 340 msec. This spread of about 200 msec reflects the complexity of these reponses.

Case II—With External Torque

From anatomical considerations, it is seen that when the foot is extremely plantar flexed involuntarily by an external torque, the achilles tendon is quite slack while the anterior tibial tendon is stretched. When the hammer strikes the slack achilles tendon the stimulus of muscle stretch reaches the spindle receptors more attenuated and after a longer latency than if the achilles tendon is taut as in involuntary dorsiflexion. This explains in part the smaller amplitude of foot angle response in initial plantarflexion as well as longer latency in response. Also contributing to the decrease of ΔFA under conditions of extreme plantarflexion is the fact that the anterior tibial muscle is being stretched nearly maximally, and will allow very little additional stretch.

The plateau in the foot angle response (with or without external loading) raises some questions as to the origin of this type of response. It appears that the plateau may be caused by an opposing stretch reflex of the antagonist, the anterior tibial muscle. Since the foot plate is free to rotate, the anterior tibial muscle is stretched by the gastrocnemius-soleus muscle contracting in the initial phase of its stretch reflex response to the original hammer blow. Although this secondary stretching of the anterior tibial muscle is fairly slow as compared to the quick stretch of gastrocnemius-soleus muscle due to hammer blow, it seems to be sufficiently rapid to reflexly contract the anterior tibial muscle. In the case of no external torque, the EMG activity in the ATM using surface type electrodes was usually observed with a latency of 40 msec after the hammer percussion and synchronous with the EMG activity in GM. On a few occasions a second spike roughly 35 msec after the beginning of the GM contraction was also noted. In case of external loading, this second EMG wave in the ATM is more frequent, particularly in those cases when the velocity of deflection is greatest. It is quite possible that the later part of the EMG activity in the ATM due to its asynchronous nature was not always sufficient to be observed via the surface electrodes. With this difficulty in mind, the secondary EMG activity can be considered as evidence for the opposing ATM stretch reflex.

Since the soleus muscle is a slow muscle and the anterior tibial muscle is a fast muscle, the time courses of their contractions are quite different. The net effect of these two antagonistic muscles is diagrammatically illustrated by the dotted line in Figure 18. This dotted line shows a dip which is not seen empirically to be significant since this would involve a lengthening of the plantar muscles at the same time as they are actively contracting, a phenomenon effectively seen only if the lengthening force is quite strong.

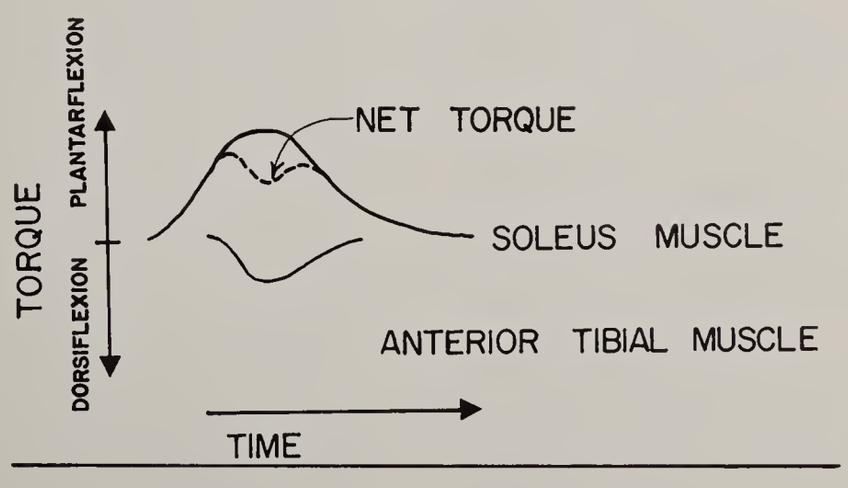

Fig. 18.—Interaction of the agonist-antagonistic muscle (soleus and anterior tibial) contractions.

Comparison with Other Methods

Three methods have been reported in the literature for recording tendon reflexes. Chaney [9] and Lambert et al [10] have measured tension essentially in the isometric condition. Time records of the isometric torque in our experiments (Figure 4) are very similar to the records given in Figure 2 of Lambert et al's paper [10]. Lawson [11] has used a "kinemometer" to measure the free achilles reflex which is essentially isotonic muscle response. This apparatus used a horseshoe magnet, a coil and a standard EKG recorder. The voltage recorded is a function of the rate of change of displacement of the foot (i.e., velocity). Gilson [12] developed an apparatus, the "photomotograph" which photoelectrically measured the displacement of the foot in timing the free achilles reflex.

Lawson [32] has compared the photocell method with the electromagnetic method. He found that the correspondence of values for contraction time showed a coefficient of correlation of less than 0.6, and the corresponding coefficient of correlation for relaxation time was less than 0.5. The linearity of these recording devices and the accuracy which should also include the dynamics of the recorder for these methods have not been reported.

Our method of recording the isotonic response (without external loading) is quite different from the electromagnetic and photocell methods. The resolution and the linearity of the displacement (rotation) measurements depend on the potentiometer used which is very good [linearity $\pm$ 0.25%] and the dynamics of the recording device is virtually eliminated, since the data is stored on a computer tape at a rate of 1000 samples per sec and plotted in slowed reruns.

Smart and Robson [15] have proposed an apparatus "oscillomink", which consists of a foot-plate and a potentiometer device somewhat similar to what we have used for isotonic responses. They observed that their tracings were essentially similar to those reported by Gilson [12], and Sherman et al [14], and by Chaney [9], Lambert et al [10], who used other methods. However, no tracings were published in their paper. Since Lambert et al [10] only measured the tension in essentially isometric condition, reporting in their paper [10] that the movement of the platform during the reflex response was less than 0.001 inch, Smart and Robson's observation was certainly incorrect.

VI. Summary

1. Isometric and isotonic reflexes have been elicited in the gastrocnemius-soleus muscle of normal men in order to study the relation between the initial conditions (tension or length), the stimulus (hammer force) and the reflex response (change in foot torque or angle).
2. In the isometric case, foot torque response is found to be directly and strongly related to hammer force, and only secondarily and inversely to initial foot torque. The time at which the maximum foot torque response occurs is shown to be a function of initial foot torque and is not dependent on hammer force or the foot torque response. This time is minimum when the initial tension (IFT) is in the plantarflexion direction.
3. In the isotonic case with no external loading, the foot angle response is strongly related to hammer force, showing both a dead band and a saturation. There is a plateau in the foot angle response which is maximum when the foot plate is about 90° with respect to the lower leg. The maximum duration of this plateau is about 120 msec.
4. In the isotonic case with external loading, the foot angle response is strongly related to the involuntary initial foot angle due to external torque. The foot angle response as a function of hammer force shows both a dead band and a saturation.
5. The plateau is the isotonic responses appears to be caused by an opposing stretch reflex of the anterior tibial muscle; this net effect is also strongly

influenced by the differing contractile properties of the agonist-antagonist pair, the soleus and anterior tibial muscles.

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ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Hass, G. M.; Landerholm, W.; and Hemmens, A.: Inhibition of Intercellular Matrix Synthesis During Ingestion of Inorganic Lead. *Am. J. Path., 50: 815-847, 1967*

By giving an excess of vitamin D to rabbits it was possible to produce calcification of arterial walls with conspicuous fibro-cellular thickening of the intima of several of the calcified arterial systems. It was also possible to produce a severe degree of osteosclerosis characterized by the accumulation of large quantities of intercellular osteoid matrix in bones. When the regimen of vitamin D was instituted in rabbits ingesting lead subacetate, the expected production of intercellular matrices in arterial intima and bone did not occur. The effect of ingestion of lead subacetate under these conditions resembled the effect of vitamin C deficiency on collagen production. There was evidence that the widespread "toxic" effects due to ingestion of lead have a common pathogenesis related to interference in production of intercellular matrices among which collagen is the best defined.

Hass, G. M.: The Pathogenesis of Human and Experimental Athero-arteriosclerosis. *In: Cowdrey's Arteriosclerosis (second edition), edited by H. T. Blumenthal, Charles C. Thomas, publisher, Springfield, Illinois, Chapt. 31, pages 689-715, 1967*

Relations between the pathogenesis of human and experimental athero-arteriosclerosis include a description of the following topics. First, the role of medial degeneration. Second, the role of medial degeneration and calcification in relationship to proliferation of the intima with narrowing of the lumen of the artery. Third, the relation between the activity of proliferation of mesenchyme in the intima and the deposition of lipids in the intima. Fourth, the relation between the level of blood cholesterol and the probability of deposition of lipids in different parts of the arterial system undergoing degenerative and regenerative reactions. Fifth, the relation between the above described effects and the probability of formation of mural fibrinous thrombi in abnormal arteries. Emphasis is placed on the differences and similarities between the experimental and human types of athero-arteriosclerosis.

Hass, G. M.; McDonald, J. H.; Oyasu, R.; Battifora, H.; and Paloucek, J.: Renal Neoplasia Induced by Combinations of Dietary Lead Subacetate and N-2-Fluorenylacetamide. *In: Renal Neoplasia, J. S. King (editor), Little Brown and Company, Inc., Chapt. 15, pp. 377-412, 1967*

When used alone in rabbits and rats the ingestion of N-2-Fluorenylacetamide (2-AAF) led to the development of tumors of the mucosa of the renal pelvis and urinary bladder. The ingestion of lead subacetate regularly produced epithelial tumors of the renal cortex of the rat but not of the rabbit. Tumors induced when 2-AAF and lead subacetate were used

together in the diet of the rat did not differ structurally or in location from those produced by the tumorigenic agents individually. However, the combination greatly enhanced the rate of appearance and development of malignancy of certain rat tumors, more particularly those of the renal cortex and urinary bladder than those occurring in the liver and brain. The resemblance between the lead-induced renal tumors and those often encountered in the human kidney justifies a search for a common pathogenesis, especially inasmuch as the specific preneoplastic nuclear changes in the rat kidney are identical with those in lead poisoning in man. Lead is presumably tumorigenic only because it modifies metabolic events and its ability to do so depends upon conditions not necessarily present in all species or in all members of any species. This directs attention, so far as the pathogenesis of the neoplasia is concerned, to interference by lead ions in the sequence of metabolic steps in the synthesis of heme.

Leavitt, F.: EEG Activation and Reaction time. *J. Exper. Psychol., 77: 194-99, June 1968.*

The covariation of reaction time and alpha desynchronization was investigated at foreperiods of 200, 500, 1500 and 4000 msec. The results demonstrated that reaction time and alpha desynchronization are significantly influenced by variations in the foreperiod condition. Reliably faster RT and maximal alpha desynchronization occurred 500 msec after the warning signal; however, within the context of the foreperiod, the two variables did not covary. A unitary underlying arousal process was rejected in favor of multiple neural arousal processes.

Whitehead, E. D. and Bush, R. B.: Abu Bakr Muhammad Ibn Zakariya Ali-Razi (Rhazes). *Invest. Urol., 5: 26-68, Sept. 1967.*

Rhazes is considered by many to have been the greatest clinician of his age. He was born about 850 A.D. at Rayy in Khorassan in northeast Persia and died about 923 A.D.

He was a prolific writer and is reputed to have been the author of at least 232 treatises on a wide variety of subjects, including philosophy, music, alchemy, chemistry, physics, astronomy, mathematics, theology, and poetry, in addition to medicine and surgery. His renown rests primarily on the voluminous and comprehensive *Kitab al-Hawi* (*The Book Which Embraces Medicine*), which has become known in Latin under the title *Continens Medicinae.* This compendium contained detailed references to the extant medical knowledge of his day in all areas of therapeutics. He is also reputed to have written the *Kitab al-Mansuri* which is a concise and practical guide to the practice of medicine and surgery, comprising ten volumes. The ninth volume called "*Nonus Almansoris, Concerning Diseases from the Head to the Feet*" became the best known and was a source of therapeutic knowledge until long after the Renaissance.

Rhazes is credited with many contributions, which include being the first to mention true distillation, glass retorts and luting in chemistry and the use of corrosive sublimate, arsenic, copper sulfate, saltpeter and borax in the treatment of disease. In addition to his classic work on measles and smallpox, he probably gave the most detailed account of curvature of the spine in his time. He wrote what is believed to be the first book devoted entirely to pediatrics. He is attributed to be the first to use wet-cupping in treating apoplexy, cold water baths in typhoid fever, the seton in surgery, animal gut for sutures and silk sutures and alcohol for hemostasis. In addition, he appears to have introduced mercurial ointments. Regarding venereal disease he introduced three novel techniques: urethral injections of jellies made from quince, psyllium seed, or honey; the use of a stylet to clear an obstructed catheter and perineal urethrotomy for impassable strictures.

Rhazes was, indeed, the greatest clinician of his age. While wedded to Galenic philosophy, he nevertheless emerges as one of the greatest disciples of Hippocrates.

Wolff, John R. and Nielson, Paul E.: The Nonpsychiatrist Physician as a Liaison Teacher of Psychiatry. *Amer. J. Psychiat., 124: 2, Aug. 1967.*

This paper is a report of three years' experience in liaison teaching of psychiatry in the curriculum of obstetrics-gynecology. The unique aspect of this program is that the teaching is primarily conducted by a nonpsychiatrist physician.

The initial step was the establishment of weekly conferences for the attending, house staff, and senior medical students, focusing on the emotional and social aspects of patients in obstetrics-gynecology and on the importance of interactions.

This liaison led to the development of an out-patient clinic in obstetrics-gynecology centering on the emotional aspects of patients who are treated within this specialty. This clinic affords a continuity of learning experience following the conferences.

A special consultation office, which is used by both patients and students seeking advice, has been established on the maternity unit. This area serves as a research center for two projects involving members of both departments.

The liaison has demonstrated that a most effective method of teaching psychiatric principles to the medical student, resident, and nonpsychiatrically trained physician can be achieved when the primary teacher is a member of that group we are seeking to instruct.

Kornel, Ludwig; Schrohenloher, Ralph E.; and Caldwell, Robert C.: Isolation from Plasma of an α_1-Glycoprotein Resembling "Orosomucoid." A Simple Method for Its Estimation in Blood and Tissues. *Arch. Biochem., 122: 280-288, Nov. 1967.*

An acid α_1-glycoprotein has been isolated from human plasma, and closely resembles "orosomucoid" as to its ultracentrifugal and electrophoretic behavior and chemical composition. However, the two preparations differed from each other immunologically. The data obtained suggest that the isolated protein is actually "orosomucoid," but probably less denatured than the preparations obtained by other procedures. A method is described for the isolation and estimation of this α_1-glycoprotein from plasma and tissues, which, owing to its simplicity, is suitable for use in routine clinical laboratories. The procedure described is also highly specific, as indicated by over 90% purity of the isolated product.

Anderson, Earl T.; Passovoy, Mitchell; and Trobaugh, Frank E., Jr.: Quantitation of Gastrointestinal Bleeding by Use of a Large Volume Scintillation Detector. *J. Nucl. Med., 7: 612-219, 1966.*

An essentially closed-system of stool collection and radioessay which involves only one specimen transfer has been coupled with sodium chromate-51 labeling of red-blood cells to provide a sensitive and accurate estimate of blood loss in feces.

After a patient's red-blood cells are labeled with ^{51}Cr, his stools are collected into one gallon tins, mixed by external agitation, transferred to low potassium glass jars, and counted in a large volume scintillation counter.

Amounts of stool blood as small as 1 ml can be detected. This should provide a practical means of estimating the amount of blood lost in stools and provide a useful clinical diagnostic procedure.

Lewis, Jerry P.; Passovoy, Mitchell; and Trobaugh, Frank E., Jr.: Transplantation Potential of Marrow Frozen at Programmed Cooling Rates. *La Greffe Des Cellules Hematopoiétiques Allogéniques Paris, 7-9, Sept. 1964.*

Using a sensitive bioassay of the repopulating potential of mouse marrow, we have studied independently five phases of the cooling and freezing curve of marrow suspended in 12% glycerol and 4% serum and make the following observations:

1. Cooling marrow from room temperature to the freezing point and varying the rate of cooling from 0.8° C to 4° C per minute does not affect marrow viability.
2. Varying the super-cooled pre-freezing plateau from 0 minutes to 16 minutes does not affect marrow viability.
3. The temperature at which freezing is initiated within a range of −8° C to −18° C does not affect the viability of the marrow suspension.
4. Prolonging the post-freezing plateau decreases the viability of marrow.
5. Following the post-freezing plateau, increasing the rate of cooling from 1° C per minute to 24° C per minute produces a significant reduction in the viability of the marrow.

In vitro studies of controlled rate cooling of bone marrow have been reported by Rowe and Rinfret.[5] These are the first reported *in vivo* studies on marrow viability varying independently each phase of the cooling curve. It is through such studies that the formulation of optimal conditions for the freezing and storage of mammalian marrow will be possible.

Anderson, Earl T.; Lewis, Jerry P.; Passovoy, Mitchell; and Trobaugh, Frank E., Jr.: Marmosets as Laboratory Animals. II. The Hematology of Laboratory-kept Marmosets. *Lab. Anim. Care, 17: 30-40, Feb. 1967.*

Abstract. Studies have been performed on the hematopoietic system of recently captured, laboratory acclimatized marmosets. "Normal ranges" as determined in this study have been compared to the normal ranges in humans and to values found in the rhesus monkey and one other study of marmosets. The similarity of marmoset hematologic values to those of humans lends support to the thesis of using marmosets as laboratory animals suitable for use in human tumor-virus research.

Lewis, Jerry P.; Passovoy, Mitchell; McFate, Patricia A.; and Trobaugh, Frank E., Jr.: The Rate of Growth and Pattern of Differentiation of Transplanted Frozen and Thawed Hematopoietic Cells. *Transplantation, 5: 435-443, May 1967.*

Murine marrow cells which have been frozen and thawed were studied for their ability to differentiate and proliferate following transplantation into isogeneic hosts. Using the hematopoietic colony technique, these cells were compared with fresh cells by injecting them into irradiated CAF_1 mice. Serial sections of hematopoietic colonies produced in the animals' spleens were studied, and the volume of the largest erythroid colony in each of these spleens was measured. The pattern of cellular differentiation and the volume of the erythroid colonies produced by thawed cells were found to be similar in every respect to those produced by fresh cells, suggesting that freezing and thawing does not affect the transplantation ability of the hematopoietic stem cells which survive these processes.

Bezkorovainy, A.: Ultracentrigal, Behavior of Transferrin in the Presence of Some Anions. *Biochim. Biophys. Acta, 126: 286-291, 1966.*

Transferrin of pooled human plasma has been found to aggregate reversibly in the presence of BrO_3^-, SCN^-, Cl^-, Br^-, and NO_3^-, giving weight-average sedimentation coefficients of from 5.50 S to 6.83 S compared to a normal s_{20}, w of 5.10 S at 0.7% concentration. The aggregation was most pronounced in the vicinity of the isoelectric point of transferrin, i.e., at pH 5.0, and was dependent on the anion, but not on the protein concentration. No aggregation was observed in the presence of acetate, formate, chloracetate, fluoride, cacodylate and sulfate at any pH value.

Bezkorovainy, A.: Comparative Study of Metal-free, Iron-saturated, and Sialic Acid-free Transferrins. *Biochim. Biophys. Acta, 127: 535-537, 1966.*

Physical parameters of iron-free and iron-saturated transferrins did not appear to be grossly different indicating little, if any, conformational change accompanying the binding of iron by the transferrin molecule. Sialic acid was not necessary for the binding of iron by transferrin.

Bezkorovainy, A. and Grolich, D.: The Behavior of Native and Reduced-alkylated Human Transferrin in Urea and Guanidine-HCl Solutions. *Biochim. Biophys. Acta, 147: 497-510, 1967.*

Molecular weight of transferrin was determined in concentrated urea and guanidine-HCl solutions, and in the presence of 0.5 M mercapto-ethanol. The molecular weight of transferrin did not drop below its native figure of 90,000. It was concluded that transferrin consists of a single polypeptide chain and does not possess a subunit structure.

Line, W. F.; Grohlich, D.; and Bezkorovainy, A.: The Effect of Chemical Modification on the Iron-binding Properties of Transferrin. *Biochemistry, 6: 3393-3402, 1967.*

Transferrin was nitrated with tetranitromethane and alkylated with bromoacetic acid. Both reactions abolished its iron-binding activity. Each iron atom required 3 tyrosyl and 2 histidyl side chains for the reaction with transferrin.

Bezkorovainy, A.: Physical and Chemical Properties of Bovine Milk and Colostrum Whey M-1 Glycoproteins. *J. Dairy Sci., 50: 1368-75, 1967.*

A glycoprotein has been isolated from bovine colostrum whey having a molecular weight near 10,000 and possessing little, if any, secondary and tertiary structure. It contained 30-40% carbohydrate consisting of sialic acid, galactose and galactosamine. Sialic acid was the terminal sugar in the oligosaccharide chain.

Ecanow, B.; Balagot, R. C.; and Santelices, V.: Possible Role of Alveolar Surfactants in the Uptake of Inhaled Gasses. *Nature, 215: 1400-67.*

Most inhalation anesthetic gases and many physiologically important gases are non-polar substances which have a very poor solubility in highly polar water. The barrier of the water layer present on the alveolar membrane is such that simple partition and diffusion mechanisms cannot possibly account for the profuse amounts of non-polar gas that is transported through lung tissue to the blood stream.

It is the thesis of this paper that solubilization of these non-polar gases proceeds thru the aggregation of the surface active molecules present in the lungs forming micelles. This mechanism occurs by the stretching of alveolar cells by inhalation which forces the surfactant molecules to migrate to the enlarged cell surface in sufficient concentration to form micelles. The lipoid portions of the micelles readily solubilizes anesthetic and physiologic gases in the quantities observed (uptake curves). Exhalation (release of pressure) reduces surface size and disrupts and disperses the micellar phase and sorbed gas into the subphase.

This hypothesis was tested by extracting dog lung surfactant and exposing it to 1% halothane (in oxygen in a tonometer). Tonometer gas concentration was determined by gas chromatography. Homogenized lung without surfactant or concentrations below micellar formation show poor absorption characteristics. Lung homogenate with its surfactant concentrated to levels forming micelles or to which a commercial surfactant of micellar concentration was added absorbed halothane in the necessary amount.

Additional support is given by reported film studies in which expansion of the film is accompanied by a sudden drop in surface tension, which is characteristic of micellar formation. Contraction of the film causes an increase in surface tension which is characteristic of micellar disruption. The authors suggest that this is a universal mechanism of any surface containing surfactant molecules in the proper concentration so that expansion of the surface aggregates the surfactant molecules and contraction disperses the individual molecules of the micelle. As an example it is not inconceivable that this type of mechanism may play a role in the uptake of molecular gases by red blood cells and plasma proteins.

Skipkowitz, N. L.; Holper, J. C.; Worland, M. C.; and Holinger, P. H.: Evaluation of an Autogenous Laryngeal Papilloma Vaccine. *Laryngoscope, 77: 1047-66, June 1967.*

In this study, 51 patients were treated with an autogenous laryngeal papilloma vaccine. Efficacy of the treatment was assessed by two methods: clinical evaluation of patient response to vaccine, and a comparison of annual operation rates before and after start of vaccine.

In the clinical evaluation, 28 patients (55 per cent) were rated as improved with vaccine therapy, 13 patients (25 per cent) unchanged, and three patients (6 per cent) deteriorated. The remaining seven patients (14 per cent) were not rated, because information was considered inadequate for a proper evaluation.

Change in annual operation rate after vaccine therapy was calculated for 37 patients for whom adequate data were available. The rate decreased in 29 patients (78 per cent), did not change in three patients (8 per cent) and increased slightly in five patients (13 per cent). Before start of vaccine therapy the mean annual operation rate for the 37 patients was 4.00; after receipt of vaccine therapy it dropped to 1.88, an average decrease of 2.12 operations per year. Statistical analysis showed that the probability of obtaining such a decrease by chance alone is less than one in 1,000.

During therapy, adverse effects attributed to the vaccine were reported for six patients (12 per cent). In five of these, the reactions (pain, induration, rash) were not considered serious enough to warrant discontinuation of treatment. Treatment was discontinued in the sixth patient, but it is questionable whether the complications that developed in this patient should be attributed to the vaccine.

Holinger, Paul H. and Brown, William T.: Congenital Webs, Cysts, Laryngoceles and Other Anomalies of the Larynx. *Ann. Otol., 76: 744, Oct. 1967.*

Commonest of all congenital anomalies of the larynx is laryngomalacia. This anomaly is characterized by a gradually increasing stridor during the first year of life which spontaneously decreases in intensity and disappears six months to a year later. It is important because stridor is the principal symptom of all obstructions of the airway, congenital and acquired, and therefore must be accurately identified to differentiate it from other conditions characterized by stridor such as laryngeal cysts, subglottic stenoses and vascular rings. Other cartilaginous anomalies are absence of the epiglottis and deformities of the cricoid such as a stenotic cricoid ring and a laryngo-esophageal cleft.

Cysts and laryngoceles are encountered originating in the neighborhood of the ventricle of the larynx. Internal laryngoceles protruding from between the true and false cords and those bulging within the aryepiglottic fold generally have some connection with the interior of the larynx. Glottic cysts and internal thyroglossal duct cysts do not have actual or potential communication with the interior of the larynx.

Webs may be a supraglottic fusion of the false cords, glottic membranes between the true cords, or fusion of the anterior portion of the true cords, or subglottic webs which are membranous, distinct from cartilaginous cricoid obstruction. Congenital glottic atresia is rarely seen in the living because only if immediately recognized at birth and relieved at once by intubation or tracheostomy can the infant survive.

Subglottic stenosis, a thickening of the subglottic structures, is common and accounts for many cases of recurring "croup" or prolonged extubation in infants tracheostomized because of the respiratory obstruction early in life.

Bilateral laryngeal paralysis is associated with cerebral retardation, a meningomyelocele or extensive birth trauma. Unilateral left cord paralysis may often be traced to anomalies of the heart or great vessels, the esophagus or the tracheobronchial tree. Unilateral right cord paralysis may be seen in an otherwise normal infant. It should be noted that the voice (cry) of an infant with bilateral recurrent laryngeal nerve paralysis is more normal than one with a unilateral paralysis; but inspiration is stridorous and a large per cent require a tracheostomy.

Vascular anomalies consist of hemangiomas and lymphangiomas, the former as capillary and cavernous, usually associated with other hemangiomas about the head and neck, the latter as laryngeal extensions of a cystic hygroma.

Knock, F. E.: N-(4-Biphenylyl)-N-(2-diethylaminoethyl)mandelamide hydrochloride: A Potent Local Anesthetic for Use with Sulfhydryl Inhibitors for Cancer Therapy. *J. Med. Chem., 10: 733, 1967.*

Selected sulfhydryl inhibitors have regressed a variety of human cancers without injury to hematologic status and wound healing or with actual improvement in hematologic status in some patients. Rapid acting sulfhydryl inhibitors of the arsenoso and iodoacetyl type can cause much pain on intravenous infusion or intratumor injection, so that potent local anesthetics for concomitant use are at times needed. For this purpose, N-(4-biphenylyl)-N-(2-diethylaminoethyl)mandelamide hydrochloride(I) has been clinically useful. In sensitivity tests against a variety of animal and human cancer cells, it can significantly potentiate the activity of clinically useful sulfhydryl inhibitors.

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Book Review

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VOL. 7 NO. 3 JULY 1968

TABLE OF CONTENTS

page

103 **Bronchial Brushing: A New Technique for Diagnosis of Pulmonary Lesions**
ROBERT S. CALLAGHAN, JURESH PATEL, and L. PENFIELD FABER

110 **The Use of Mithramycin in Malignancy-associated Hypercalcemia. A Preliminary Report**
NANCY J. GUBISCH, CHARLES P. PERLIA, JANET WOLTER, MARGARIDA M. DEDERICK, and SAMUEL G. TAYLOR, III

116 **Hepatic Granulomas Following Sulfisoxazole Administration**
HOWARD J. ROSENBLATE, ARMANDO SUSMANO, and A. WILLIAM HOLMES

121 **Recent Advances in the Pharmacology of Parkinson's Disease**
HAROLD L. KLAWANS, JR.

124 **Book Review**
FREDERIC A. DEPEYSTER

125 **Abstracts**

BRONCHIAL BRUSHING: A NEW TECHNIQUE FOR DIAGNOSIS OF PULMONARY LESIONS*

Robert S. Callaghan†
Juresh Patel‡
L. Penfield Faber§

Bronchoscopy and cytologic examination of bronchial washings and sputum are well established methods of diagnosing bronchogenic carcinoma. In many cases, however, the pulmonary lesion is peripheral and inaccessible to the bronchoscope, and sputum is scanty or absent. Investigators have recently developed techniques whereby cells can be obtained for cytologic examination from these peripherally located pulmonary lesions. In 1965, Hattori *et al.*[1] reported the use of small, non-disposable nylon brushes inserted through a bronchial catheter to obtain cells from peripheral areas. A modification and expansion of this technique has been devised and reported by Fennessy.[2,3] We believe the latter technique to be a valuable diagnostic aid and herein describe our preliminary experience and the encouraging results obtained.

TECHNIQUE

Bronchial brushing is most commonly done following bronchoscopy when it is felt the results of the bronchoscopy will fail to establish a diagnosis. If bronchoscopy and bronchial brushing are planned and the endoscopist is able to biopsy the lesion through the bronchoscope, bronchial brushing is not done. If necessary, the brushing can be done later as a separate procedure without repeating bronchoscopy.

Upon completion of bronchoscopy, a small rubber catheter is left in the appropriate main bronchus and the remainder of the procedure is done under fluoroscopic control. A flexible Seldinger metal guidewire is inserted into the bronchus through the rubber catheter, which is then withdrawn. A preshaped, sterile bronchial catheter¶ is then threaded over the guidewire and the guidewire is removed. Several catheters (Fig. 1) are available which have their distal five centimeters preshaped with curves appropriate to enter the different lobar and segmental bronchi. The rigidity of the

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¶KIFA catheter tubing (size 8F) obtained from U.S. Catheter and Instrument Corporation, Glen Falls, New York.

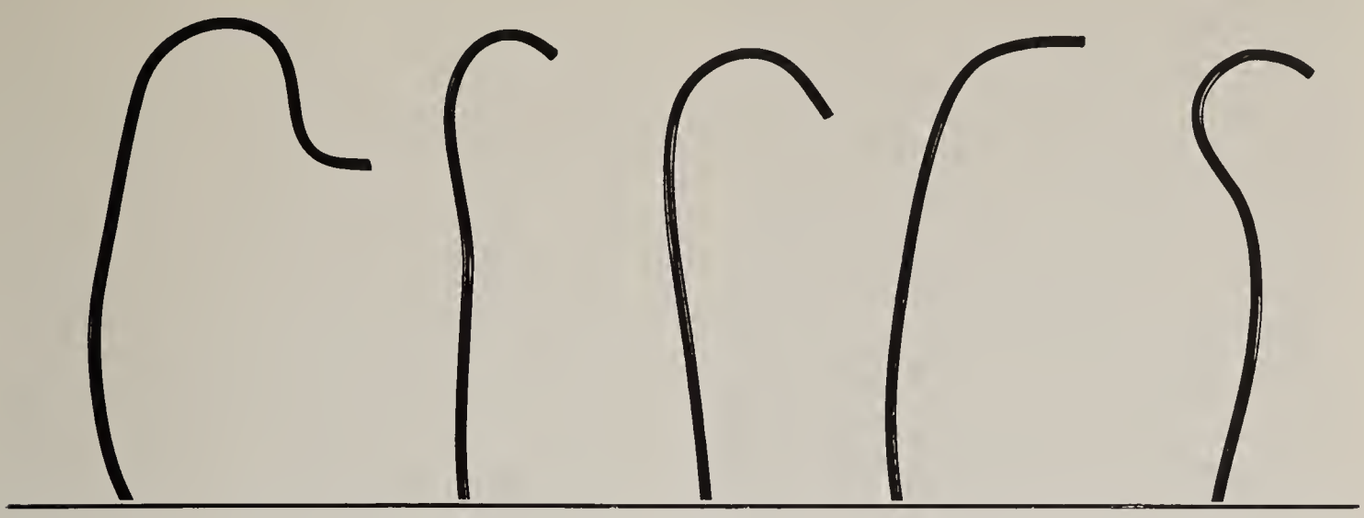

Fig. 1.—Bronchial catheters preshaped to fit selected lobar or segmental orifices.

guidewire straightens the curve of the bronchial catheter and the curve is reassumed when the guidewire is withdrawn.

When the catheter is demonstrated by fluoroscopy to be in the proper lobar or segmental orifice, a Fennessy bronchial brush# (Fig. 2) is introduced and advanced until it is seen fluoroscopically to be in the lesion. A cellular specimen is then obtained from this site, and the brush is withdrawn. Cytology smears are promptly made and fixed in Papanicolaou ether-alcohol solution. The slides are later subjected to routine cytologic scanning and evaluation.

Further studies can be done while the catheter is located in the target bronchus. Saline irrigation and aspiration can be done to collect material for culture or further cytologic study. Also, contrast material is often injected, and selective bronchograms are made to clarify the local anatomy.

Anesthesia for this procedure is that used for bronchoscopy, optionally augmented by topical application of 1 ml. of 10% cocaine through the curved catheter into the lobar or segmental bronchus.

DISCUSSION

Bronchial brushing was first performed at Presbyterian-St. Luke's Hospital in August of 1968. Thirteen patients, ranging in age from 33 to 71, have had this procedure performed with no morbidity. Eight of these patients were strongly suspected of having bronchogenic carcinoma because of typically abnormal chest x-rays. All eight were studied by bronchoscopy, bronchial washing, and cytologic examination of sputum specimens. In only one of the eight was the diagnosis of carcinoma established by these routine methods. In five of the eight patients, the diagnosis of carcinoma was made *only* by bronchial brushing. Thus, bronchial

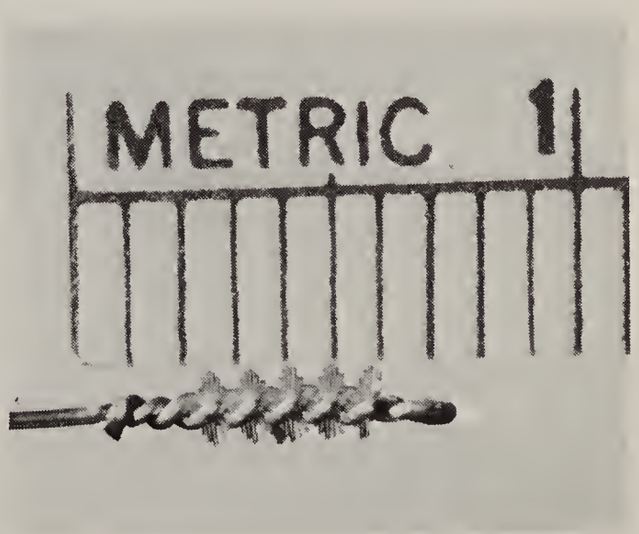

Fig. 2.—Tip of 2 mm. diameter Fennessy bronchial brush with nylon bristles.

#Mill-Rose Company, Mentor, Ohio.

brushing increased the preoperative positive diagnostic percentage from 12% to 75%. Two patients required thoracotomy to make the diagnosis of carcinoma. The other five patients in this series were proved to have benign inflammatory lesions.

In the series reported by Fennessy[3] of over 200 bronchial brush or forceps biopsies, a positive result was obtained in 64% of patients with primary lung cancer. His efforts were less effective in patients with metastatic cancer, where 44% were diagnosed in this manner.

Fry[4] used the technique of bronchial brushing on a series of patients, 38 of whom were proved to have cancer. From this group, a positive cytology by brushing was found in 68%.

REPORT OF CASES

The following cases from our own series illustrate situations where bronchial brushing is a useful diagnostic procedure.

Case 1. E.P., a 60-year-old, white male, was admitted with a history of having a "spot on the lung" found on routine chest x-ray. The patient was asymptomatic and this examination was prompted by the early death of a business associate. He had smoked two packs of cigarettes per day for forty years. Physical examination and laboratory work-up were completely normal. On the chest x-ray (Fig. 3) there is a lesion in the right upper lobe suggestive of bronchogenic carcinoma. Cytologic study of sputum specimens was negative for cancer, and

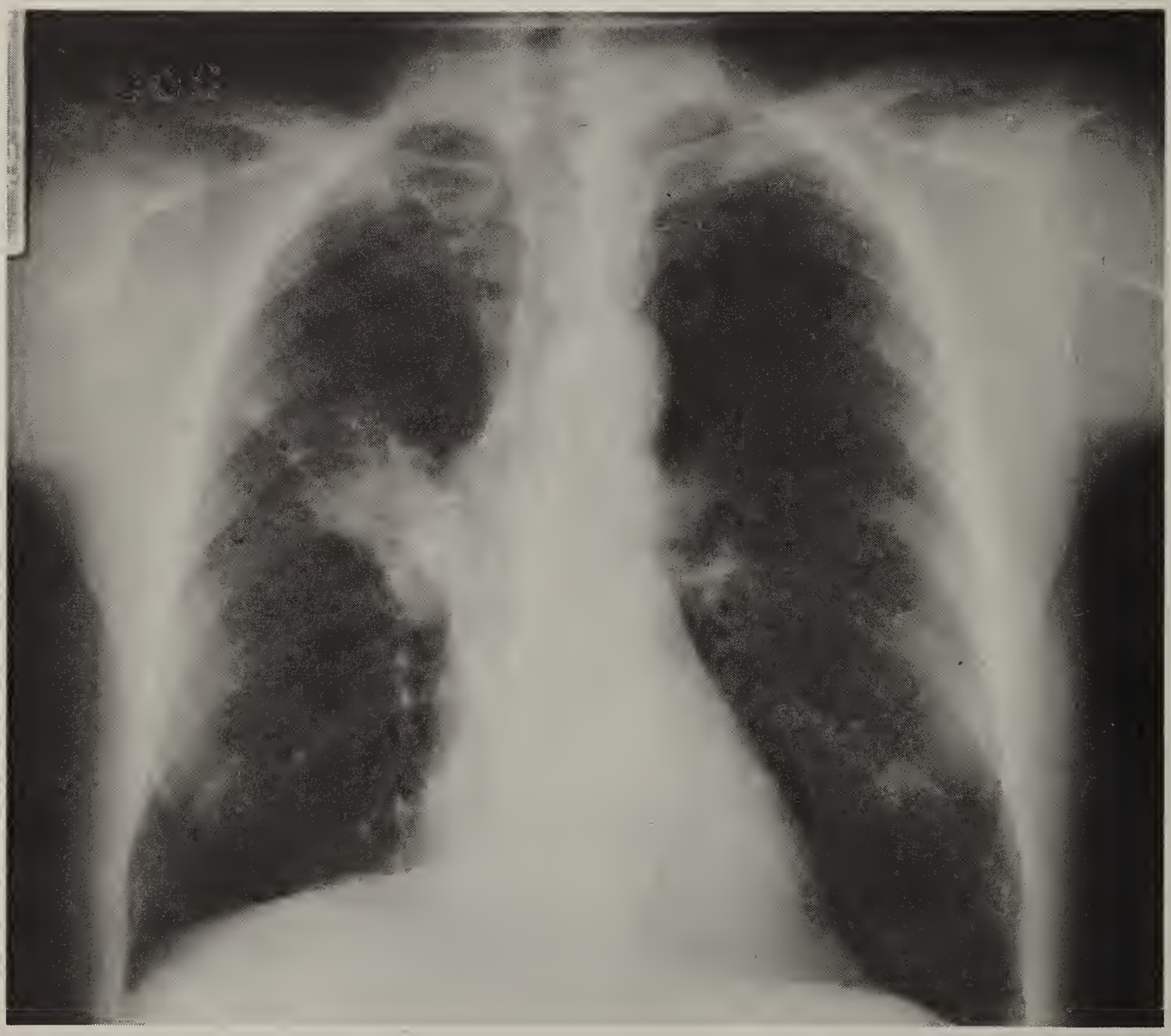

Fig. 3.—Chest x-ray revealing right upper lobe lesion.

bronchoscopy was done. At the time of this procedure, there was distortion of the anterior segmental orifice of the right upper lobe. Bronchial brushing was then performed. The bronchial brush is seen to be in the lesion (Fig. 4). The cell block from the bronchoscopic aspirate was negative, but a positive diagnosis of carcinoma was made on cytological examination of the smears made from bronchial brushing (Fig. 5). Additionally, a selective bronchogram of the right upper lobe showed the obstructed orifice of the anterior segmental bronchus. In this situation a firm diagnosis of bronchogenic carcinoma was established only by bronchial brushing. Thus, it was possible to plan the appropriate operation and avoid the need for surgical violation of the tumor by biopsy prior to resective surgery.

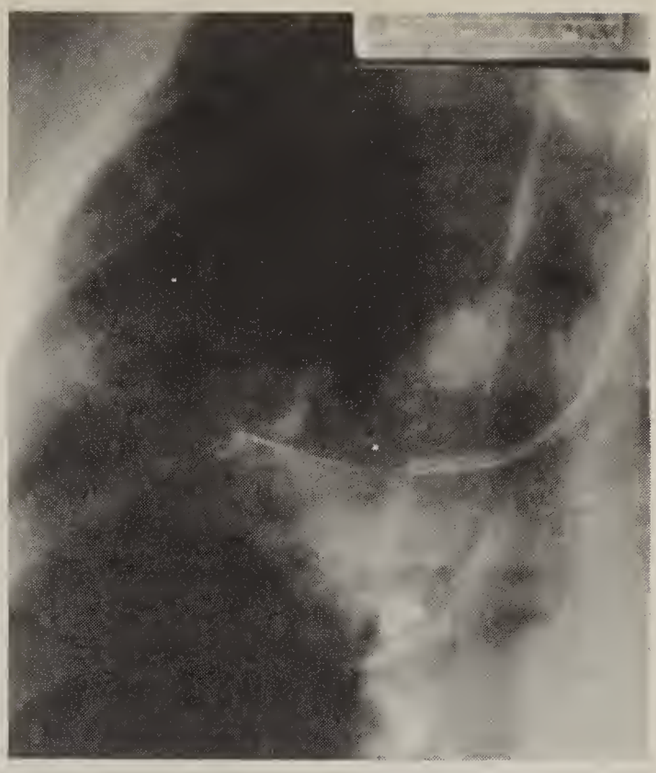

Fig. 4.—Bronchial brush is seen in the lesion, having been passed through the preshaped catheter.

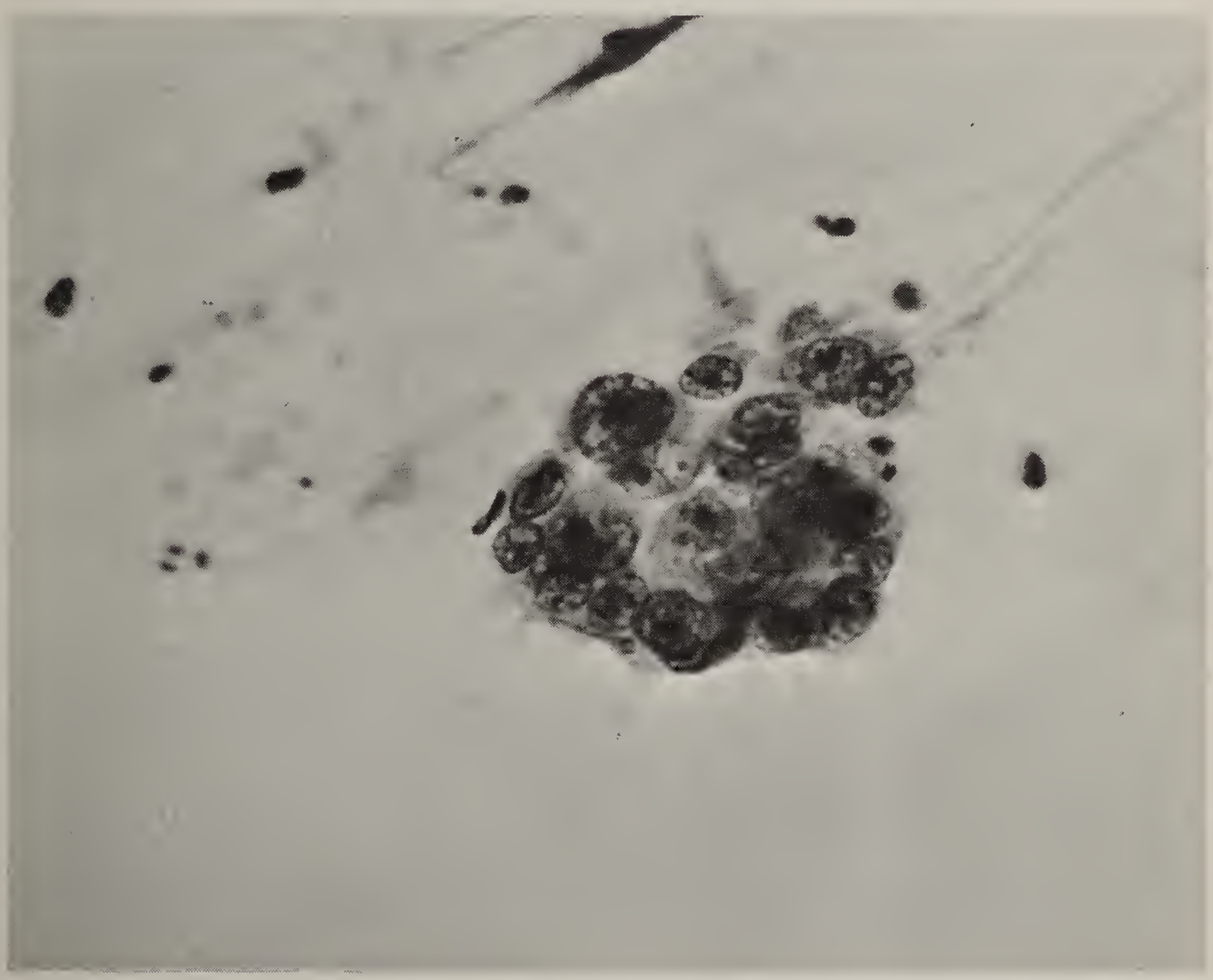

Fig. 5.—Malignant cells are clearly identified on cytologic smear from bronchial brushing.

Case 2. L.K., a 46-year-old, white male complained of hoarseness of four months' duration. On physical examination there was a high-pitched, inspiratory wheeze along the left sternal border anteriorly. The chest x-ray showed a mediastinal mass on the left and an irregular infiltrate in the left upper lobe (Fig. 6). At bronchoscopy, the left vocal cord was paralyzed, there was widening of the coryna, and the left mainstem bronchus was involved by compression stenosis to such an extent that the bronchoscope could not be advanced. The cell block of bronchoscopic washings and sputum cytology were negative for malignant cells. A bronchial brushing procedure was then done, and the cytology from this examination confirmed the suspicion of bronchogenic carcinoma. The bronchoscope could not be introduced into the area of the pathology, yet a diagnosis was made by bronchial brushing. Thus, this patient, who was inoperable because of vocal cord paralysis and mediastinal extension, did not have to undergo diagnostic thoracotomy before radiation therapy could be started.

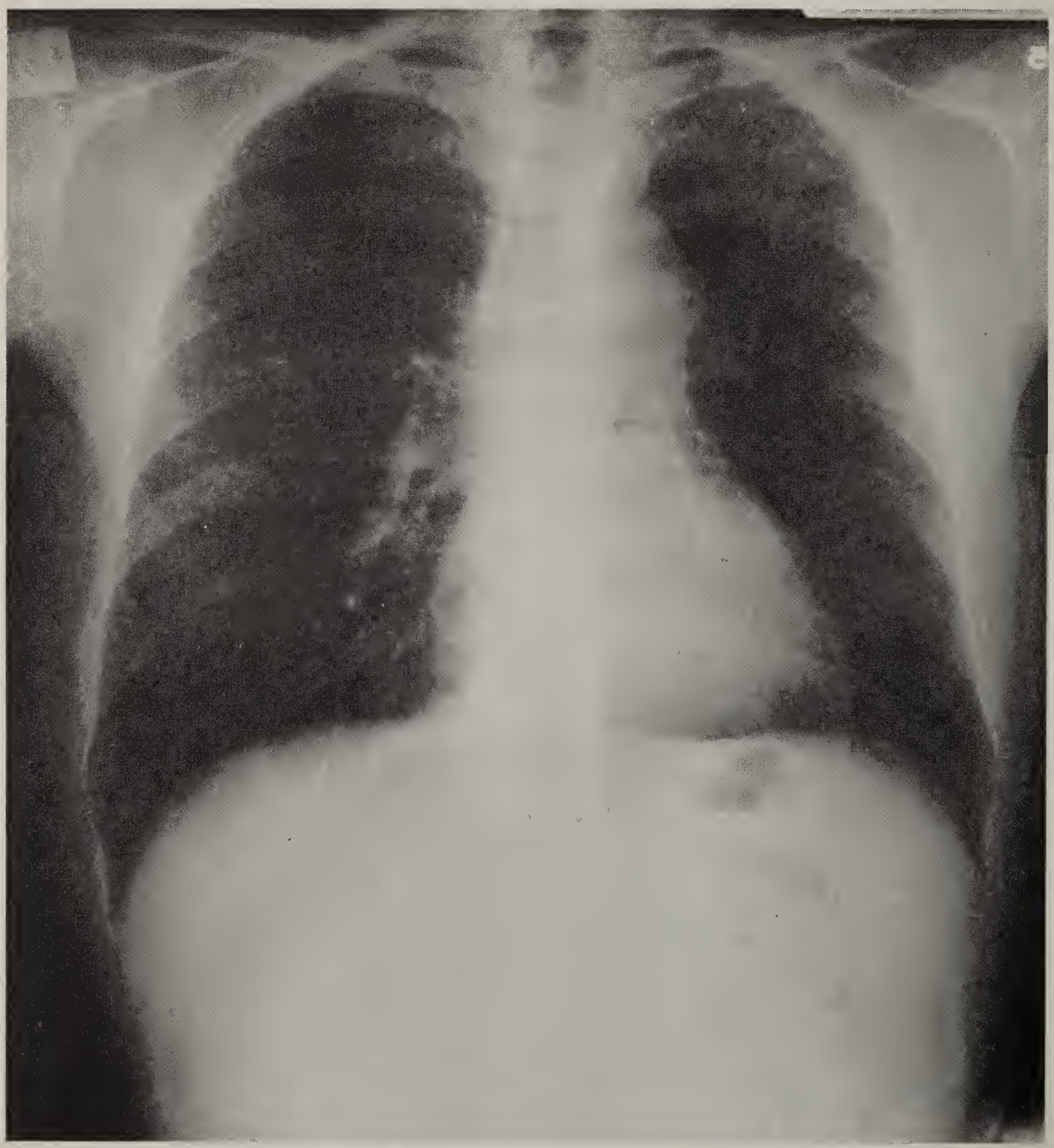

Fig. 6.—Chest x-ray showing hilar enlargement. The patient has left vocal-cord paralysis.

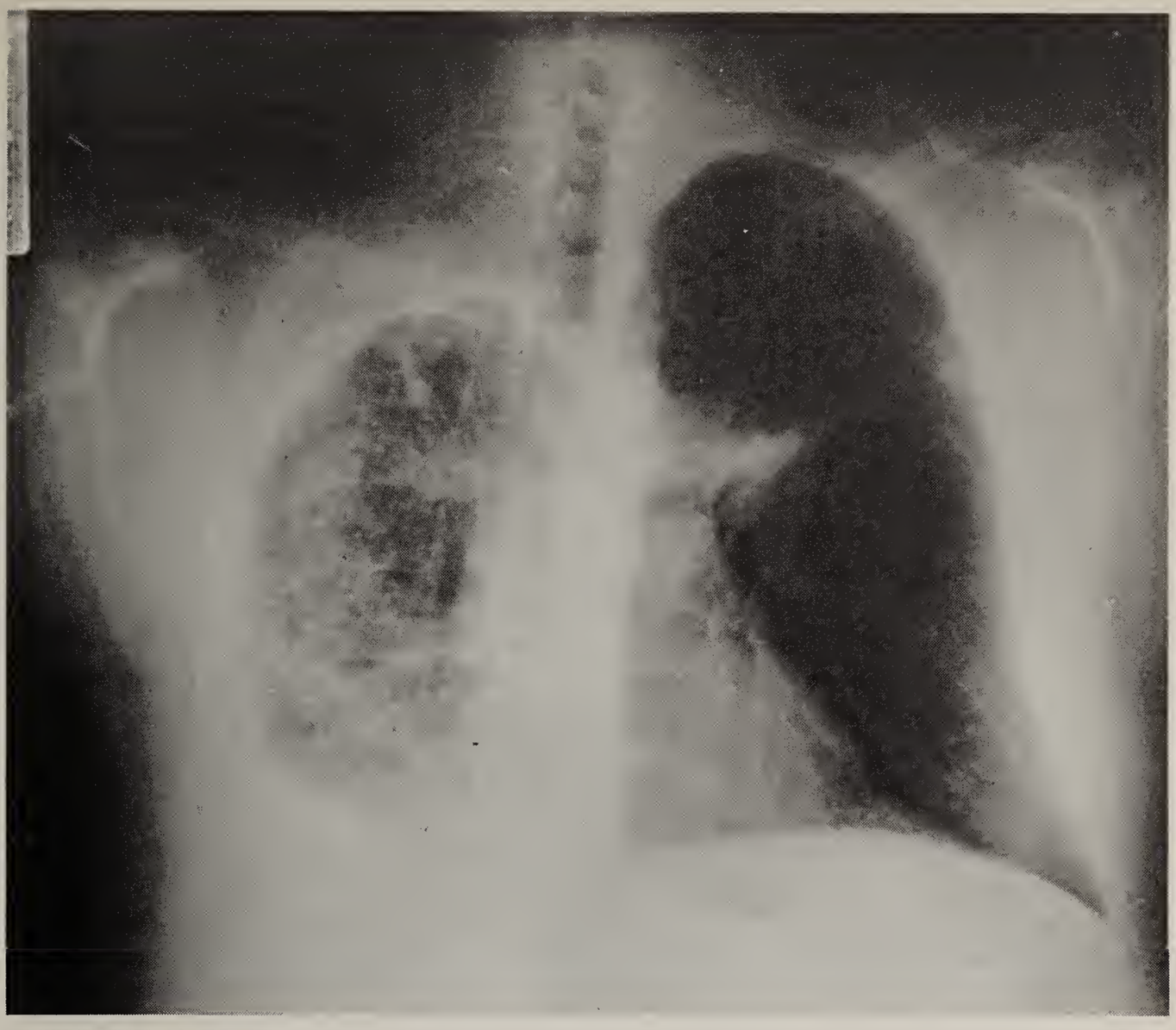

Fig. 7.—Chest x-ray showing evidence of old pulmonary and pleural tuberculosis on the right, and hilar enlargement on the left.

Case 3. L.J., a 53-year-old, white male with far-advanced, inactive tuberculosis was admitted with a one-month history of recurrent cough and hemoptysis. The chest x-ray showed an irregular mass in the left hilum. There was a history of smoking one pack of cigarettes per day for 30 years. On physical examination there were inspiratory and expiratory wheezes at the right apex, as well as diminished breath sounds over the area of the left upper lobe. Laboratory work-up was normal except for the chest x-ray (Fig. 7). At bronchoscopy the left main stem bronchus was narrowed, the orifice of the left upper lobe was compressed, and bloody secretions were seen to come from it. Because of the inaccessibility of the upper lobe bronchi, bronchial brushing was done following bronchoscopy (Fig. 8). Selective bronchogram of the left upper lobe was also done, revealing obstruction of the apical posterior and anterior segmental orifices (Fig. 9). The cell block from the bronchial aspirate was negative but the smears from bronchial brushing confirmed the diagnosis of bronchogenic carcinoma. Immediate surgical therapy for this malignancy was considered inadvisable because a pneumonectomy would most likely have been necessary, and he could not survive with only his poorly functioning right lung. Therefore, a course of preoperative irra-

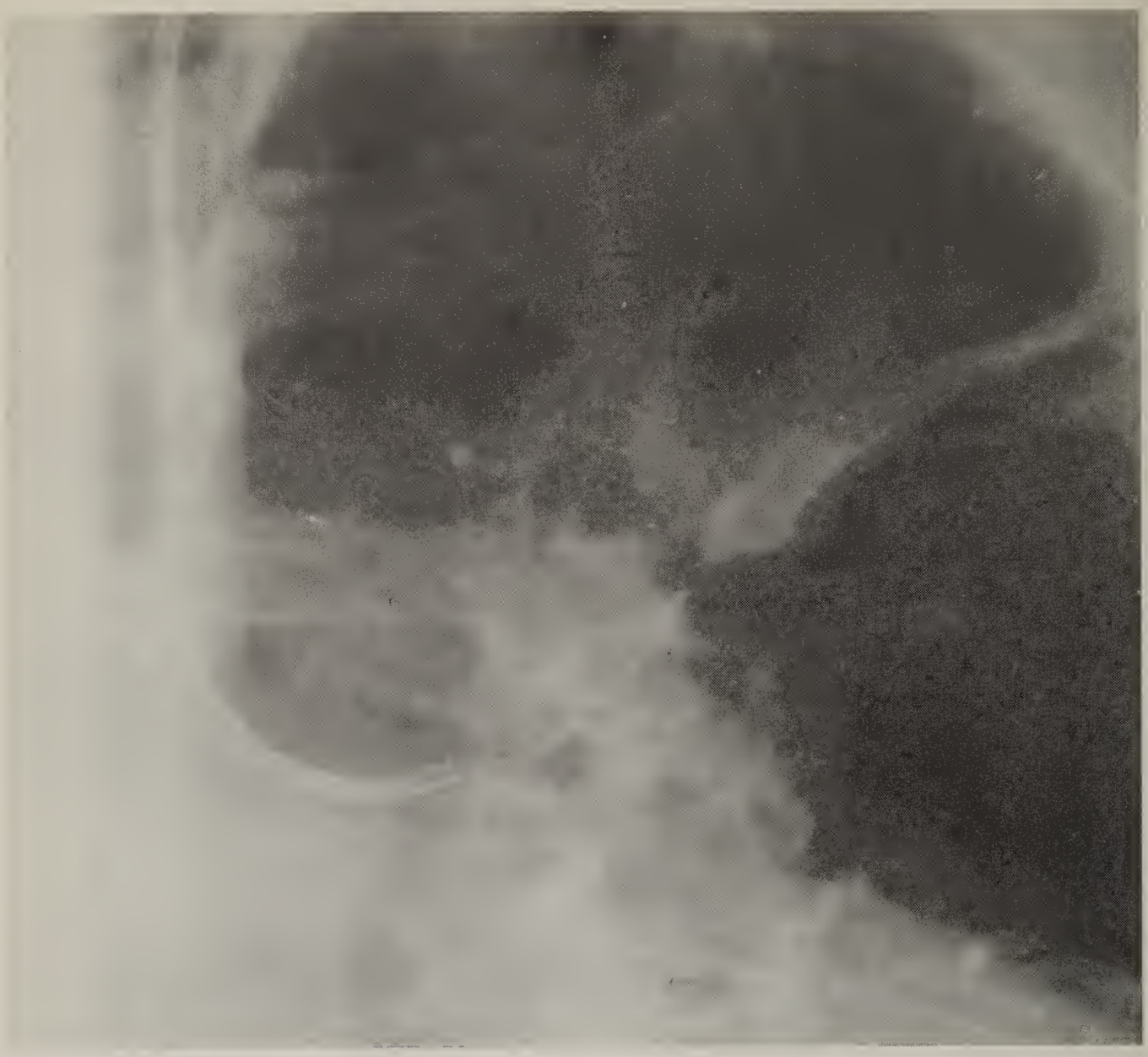

Fig. 8.—Bronchial brush positioned in the pulmonary lesion.

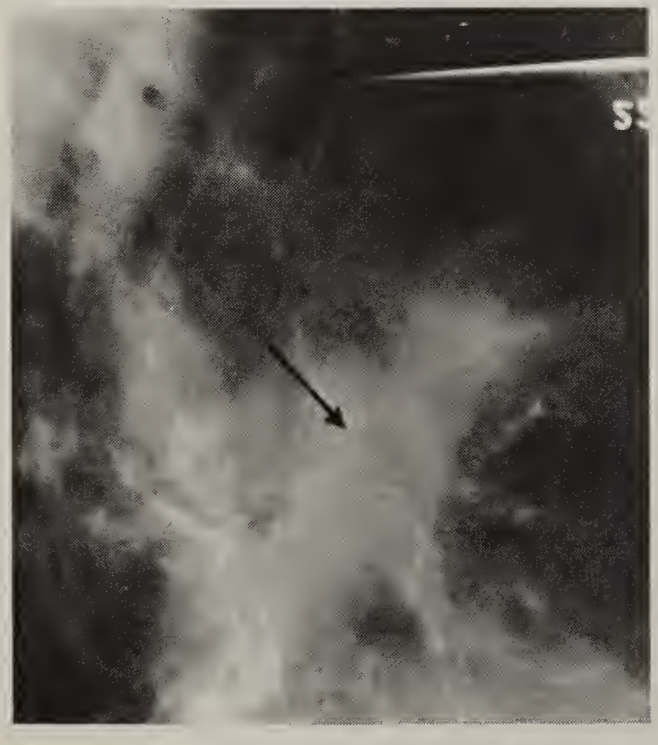

Fig. 9.—Bronchogram showing total obstruction of superior division of left upper-lobe bronchus.

diation is now being delivered, and a sleeve lobectomy is planned for the future.

There has been occasional morbidity reported with bronchial brushing.[3,4] Slight hemoptysis and transient fever have been the most common adverse effects. We have had no morbidity in our series, and no serious complication or mortality has been reported in any series.

There are many advantages to bronchial brushing. It is a simple procedure which is well tolerated and it is inexpensive for the patient. In several of the cases in our series, the diagnosis of carcinoma has been made early and the patient's hospital stay has been shortened.

In patients with extensive bronchogenic carcinoma, a tissue diagnosis must be obtained before palliative radiother-

apy or chemotherapy can be given. A thoracotomy must be done to obtain this diagnosis in those patients where all other diagnostic efforts have failed. These patients are often in a high-risk surgical group, for many are debilitated as a result of their disease. A significant percentage of this group of patients will be spared thoracotomy when the diagnosis is established by bronchial brushing. Palliative therapy can then be instituted without further study or delay. Similarly, in the patient with less extensive disease who should have preoperative irradiation before resective surgery, a diagnosis made by bronchial brushing can eliminate the need for a diagnostic thoracotomy.

The cytology smears are of excellent quality, are easily interpreted, and the histology of the malignancy often can be classified from the smear alone. Tumor cells are much more readily identified from the brushing slides (Fig. 5) than from cell block preparations.

The role of bronchial brushing in the diagnosis of inflammatory pulmonary lesions needs to be further clarified. Although it has been of little benefit in our series, tuberculosis and blastomycosis have been diagnosed in other series.[3,4] At the present time, brushes can be smeared and cultured in the microbiology laboratory when this is indicated.

SUMMARY

Bronchial brushing is a safe and inexpensive procedure and is a valuable adjunct in making the diagnosis of pulmonary malignancy. A significant group of patients with bronchogenic carcinoma, undiagnosed by conventional methods, will have a diagnosis made by bronchial brushing.

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THE USE OF MITHRAMYCIN* IN MALIGNANCY-ASSOCIATED HYPERCALCEMIA. A PRELIMINARY REPORT†

Nancy J. Gubisch‡
Charles P. Perlia§
Janet Wolter ¶
Margarida M. Dederick‡
Samuel G. Taylor, III#

Hypercalcemia is the most frequent and life-threatening metabolic aberration associated with malignant tumors, and may be seen with or without demonstrable bone involvement. Of primary importance in its control is the fact that it can occur well before the end stage of disease. Proper management requires maintaining a high urine output and limiting calcium intake. In addition, a number of agents have been found that are clinically useful, although not universally successful, in reducing an elevated serum calcium.[1,2,3,4] We would like to add the antitumor antibiotic, Mithramycin, to that list.

The use of Mithramycin (MTM) for hypercalcemia has been independently suggested by Parsons and others.[5] They observed a group of patients who were being treated with MTM as an antitumor agent in the usual course form which consists of eight to ten days of continuous drug infusion at 25 μg/kg/day. During this time they noted a decrease in the serum calcium of all patients whether the initial values were normal or elevated.

Our experience took direction from a young man whose clinical situation demanded treatment as an outpatient. We were delighted when his hypercalcemia showed a prompt and sustained response after one bolus injection of MTM which was only one-tenth the average tumor therapeutic dose. Centering on the clinical ease of the bolus injection, the minimum effective dose was sought. Of 12 patients who received the drug after a

*The Mithramycin used in this investigation was supplied through Theodore J. Medrek, M.D., of the John L. Smith Memorial for Cancer Research, Pfizer Laboratories, Division Chas. Pfizer & Co., Inc., Maywood, N.J., where it was produced under contract PH 43-64-50 with the Cancer Chemotherapy National Service Center, National Cancer Institute.

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three-day baseline study during forced hydration, only two moribund patients failed to show any response. Figures 1, 2 and 3 illustrate types of individual responses.

Figure 1 spans an eight-month period and documents three of the more closely followed episodes of hypercalcemia in our first patient who was initially seen presenting with renal insufficiency, lytic bone lesions, and a testicular mass, histologically seminoma. The initial elevation of serum calcium occurred in the hospital. After five days of prednisolone, 200 mgm. daily, intravenously, without a response, MTM 20 μg/kg was given with a response within 24 hours. Subsequent episodes were controlled with a bolus of MTM without the addition of prednisolone. In each instance, there was a concomitant drop in serum phosphorus, and as the hypercalcemia was controlled, the serum creatinine approached normal.

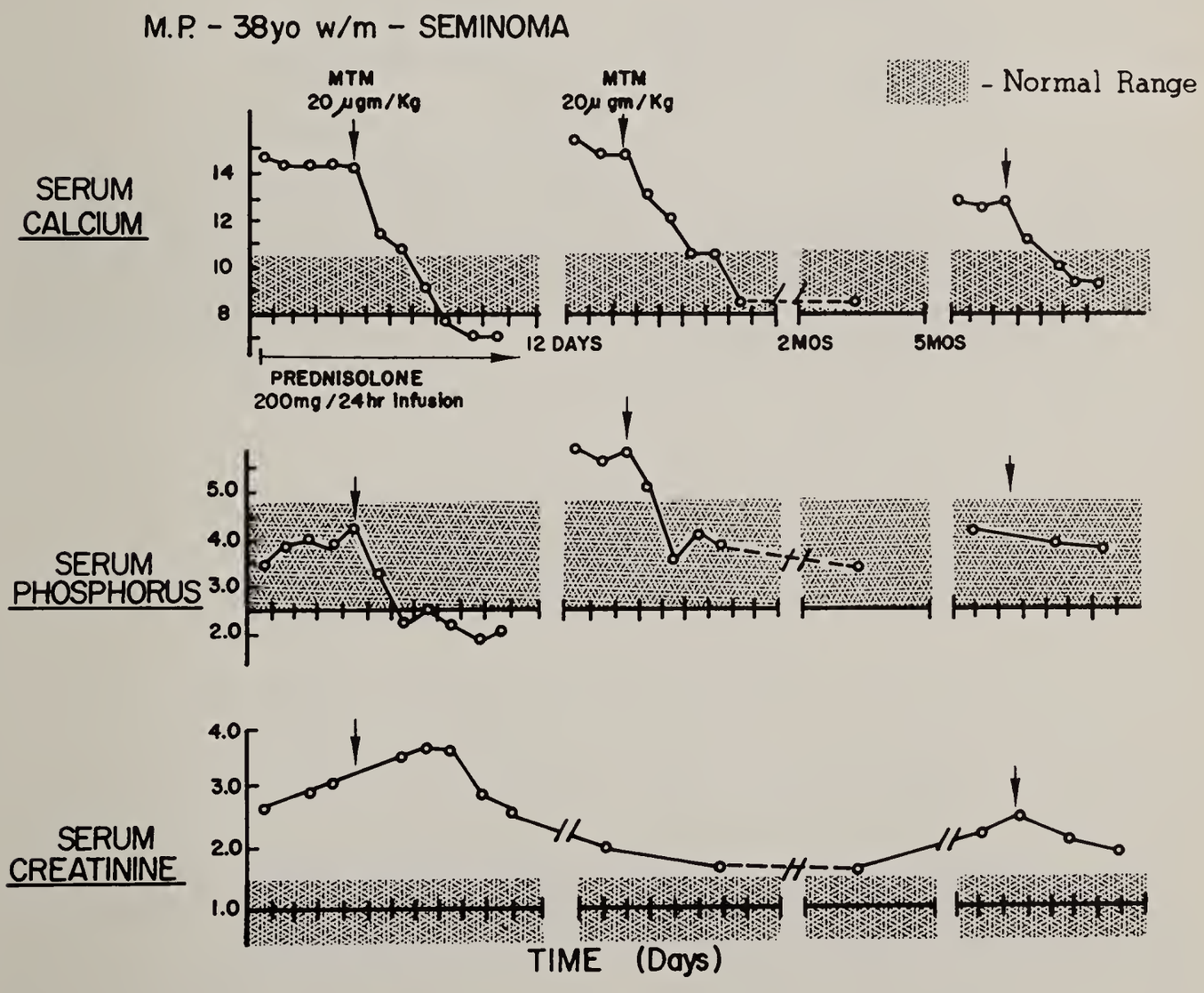

Figure 1

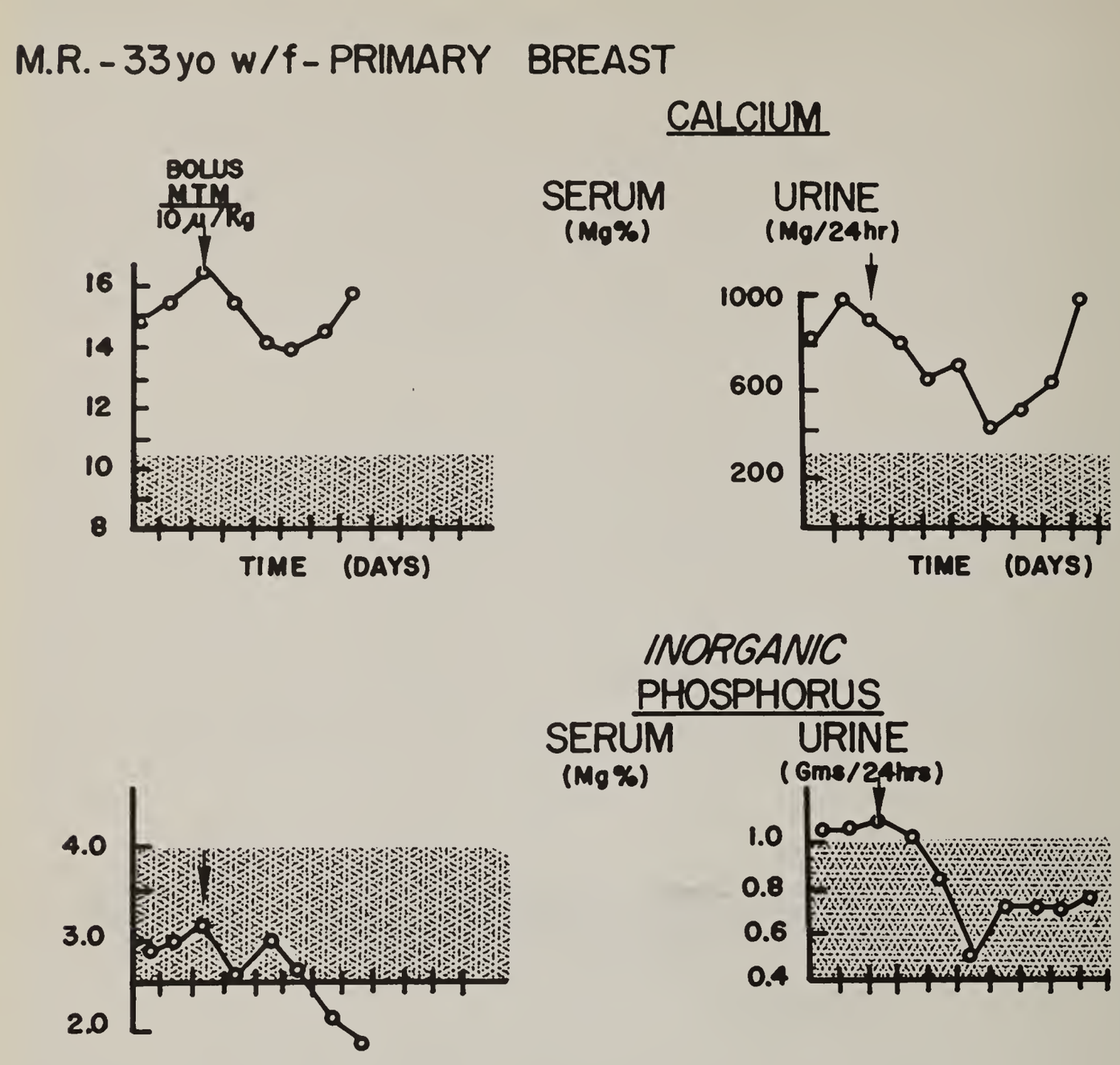

Figure 2

Figure 2 records the response in a young woman with a primary inoperable breast carcinoma, a large tender liver, and lytic bone lesions. Renal function was normal. In this patient a smaller dose of MTM, 10 μg/kg, had an incomplete and unsustained effect on serum calcium. The decrease in urinary calcium and phosphorus was proportionately greater, but also unsustained. With a subsequent dose of 20 μg/kg (not shown) the serum calcium dropped into normal range.

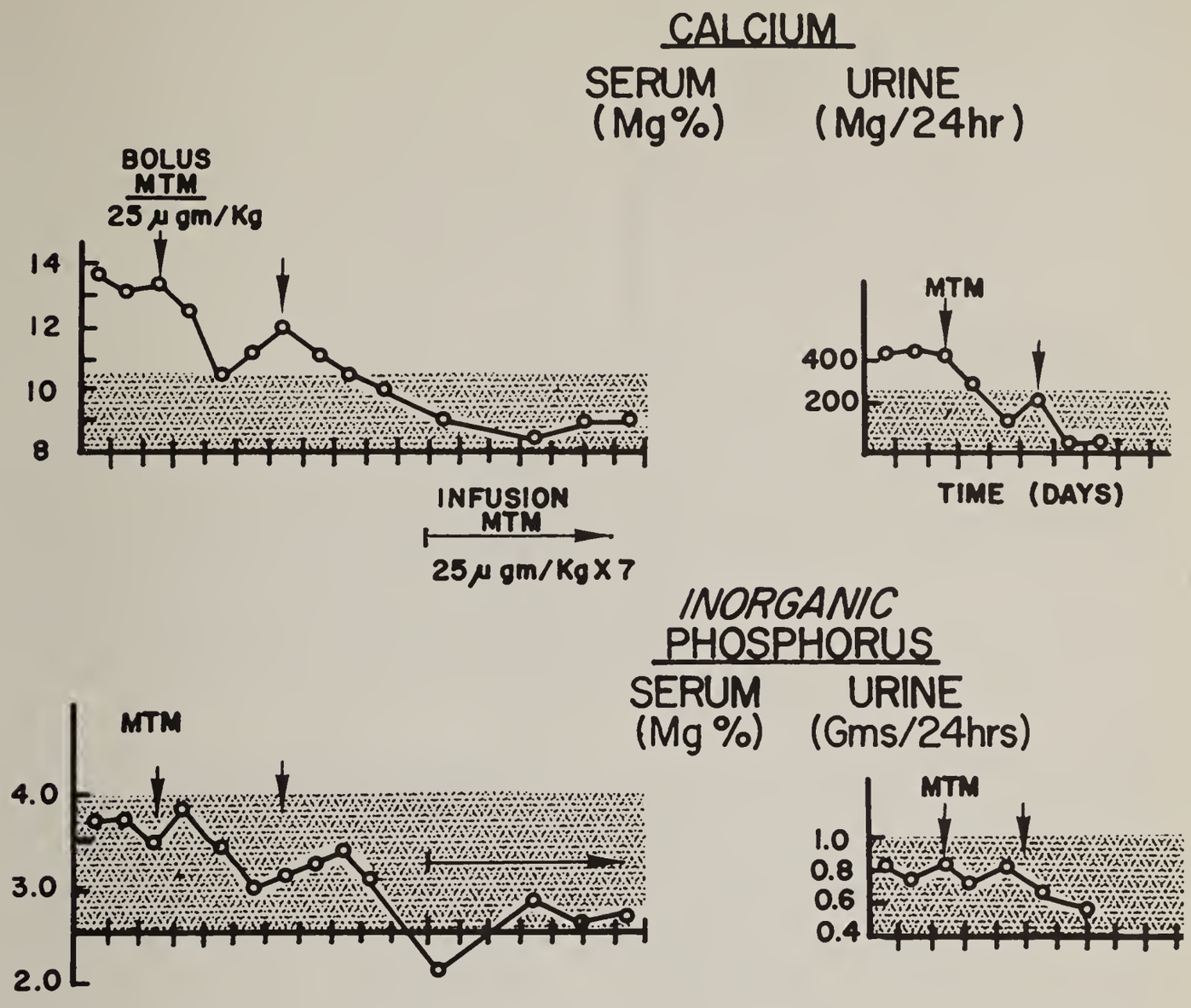

Figure 3

Figure 3 presents a patient with multiple pulmonary and lytic bone lesions. A bone biopsy revealed metastatic adenocarcinoma. An abnormal intravenous pyelogram suggested that the primary tumor was in the kidney, although it was never demonstrable histologically. Renal function was abnormal. With a bolus injection of 25 μg/kg, there was a lowering of serum calcium at 12 hours, but the response was unsustained. Another injection at this same dose brought the serum calcium within normal range. At this point it was decided to give a tumor therapeutic dose of MTM, and the patient received 25 μg/kg daily for seven days as a continuous infusion; during this time the serum calcium remained normal. As in all patients studied, the drop in urine calcium excretion reflected the drop in serum calcium.

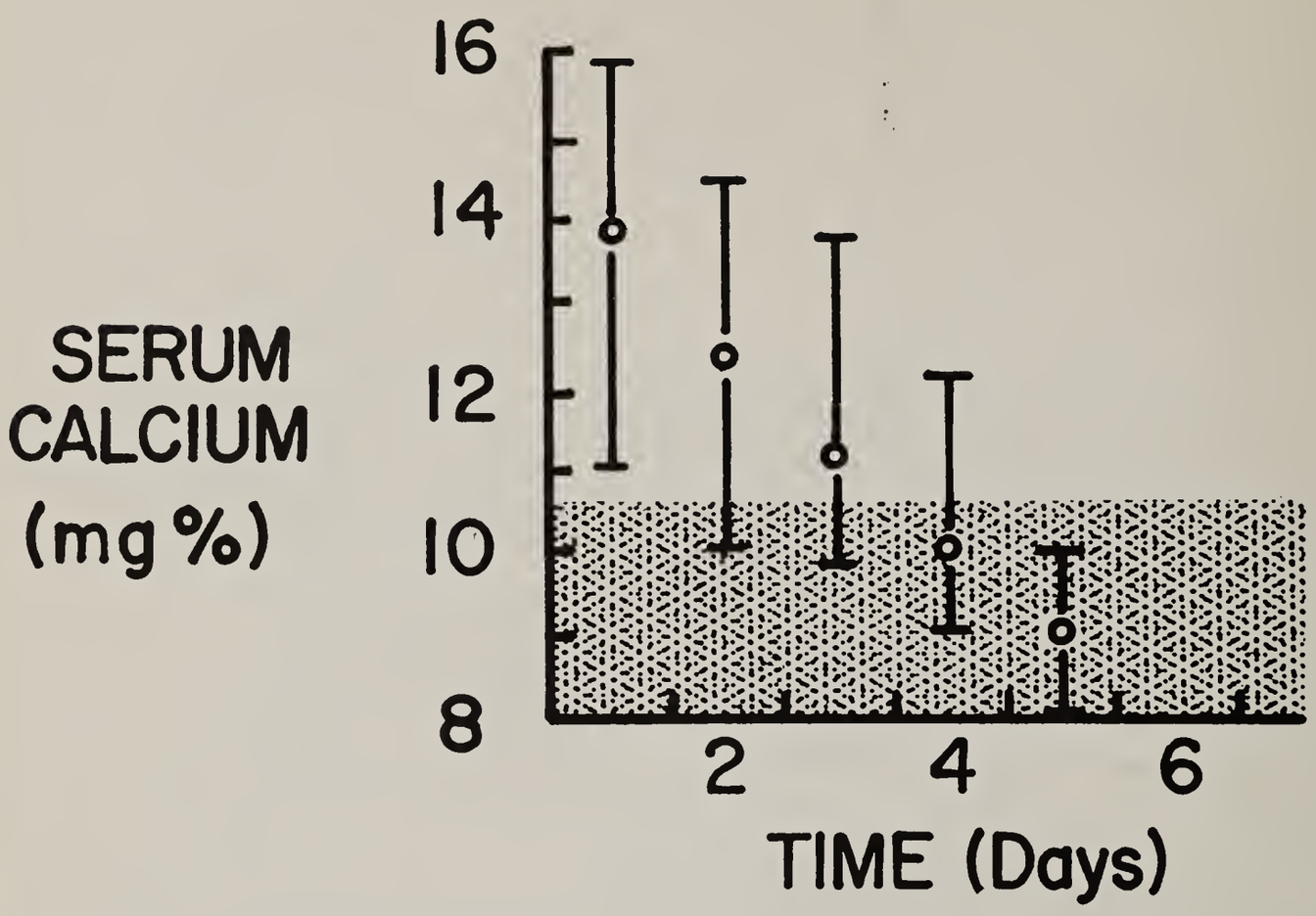

Figure 4

Figure 4 is a composite of nine trials in six patients and characterizes the fall of responsive hypercalcemia after a single bolus injection of MTM. The dose varied from 5 to 20 μg/kg. The range and mean of the daily calcium values are shown. On day one, MTM was given and the calcium level just prior to administration is recorded. A drop is noted by day two; the normal range is approached by day four; the maximum response is seen by day five. In one instance the calcium dropped to 7 mg. per 100 ml. on day six, but no lower values than this have been recorded. In six trials normal levels were maintained for at least ten days.

We have made no attempts to study the nature of the hypocalcemic effect. In studies on rats, Rothschild[6] demonstrated that MTM inhibits bone resorption in the presence or absence of Parathormone (PTH). From the marked increase in phosphate clearance by the kidney and decrease of serum calcium and phosphorus and urine calcium, Jacobson[7] proposed that in humans MTM blocks the peripheral action of Vitamin D. Adding studies of hydroxyproline excretion, Parsons postulated that MTM blocks the peripheral action of PTH on bone and gut. The effect could be direct or indirect through Vitamin D; it was noted that high doses of Vitamin D did not reverse the block. *In vitro* inhibition of RNA synthesis by MTM has been recently restudied by Northrop.[8]

CONCLUSION

Mithramycin can be an effective agent for the treatment of hypercalcemia. No toxicity was seen with the doses used; the degree and duration of response appear dose-related, but the initial calcium level is not a consistent guide to the dose needed. The study of these effects may promote further understanding of calcium metabolism, particularly in relation to neoplasms.

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HEPATIC GRANULOMAS FOLLOWING SULFISOXAZOLE ADMINISTRATION*

Howard J. Rosenblate†
Armando Susmano‡
A. William Holmes§

INTRODUCTION

The ease and safety of diagnostic needle biopsy of the liver have made it an almost routine procedure. Of 178 needle biopsies in our hospital during the years 1965 and 1966, nine specimens (5%) showed hepatic granulomas. The discovery of hepatic granulomas opens a wide range of diagnostic possibilities to the clinician. If the histological study of the granuloma together with the laboratory investigations does not indicate a specific etiology for the granuloma one must arrive at a probable diagnosis based on the information that is available. Most commonly, the diagnosis of either tuberculosis or sarcoidosis is made depending on the results of the tuberculin skin test and other, largely non-specific, data.

A case is described to illustrate a rather common clinical situation in which a non-specific hepatic granuloma was attributed to sarcoidosis. It is felt that the patient almost certainly was suffering from allergic granulomatous hepatitis due to sulfonamide allergy.

CASE REPORT

B.S., a 32-year-old Negro female was admitted to Presbyterian-St. Luke's Hospital on March 26, 1966 because of dark urine, generalized pruritus, fever, chills, myalgias, headache, nausea, anorexia, and arthralgias. Two days prior to admission a urinary tract infection had been diagnosed and therapy with sulfisoxazole¶ was begun. She had developed febrile reactions to sulfonamide compounds which were prescribed for two previous urinary tract infections developing 18 months and 9 months prior to admission. She denied contact with persons having tuberculosis, hepatitis, or other infectious diseases.

The patient had an oral temperature of 104°F. The skin showed evidence of excoriations but a dermatitis was not present. She had mild scleral icterus. The abdomen was mildly distended and diffusely tender to deep palpation. The liver edge was not felt but there was dullness to percussion two centimeters below the right costal margin. The spleen was not palpable, and lymphadenopathy was not present. The patient exhibited bilateral

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¶In the form of Gantrisin, Roche Laboratories, Nutley, New Jersey.

costovertebral-angle tenderness. Examination of the extremities revealed tender ankles and knees without redness or swelling of these joints.

The patient was observed without treatment, and her fever subsided by the fourth hospital day. Because pyuria (25-30 WBC/HPF) was demonstrated on repeated urinalyses, sulfisoxazole, 500 mg. four times a day was started, and she received a total of five doses on that and the succeeding day. Three hours after the first dose was taken the patient's oral temperature rose to 101° F. The same symptoms with which she had originally presented recurred and did not abate until two days after the sulfisoxazole was discontinued. The standard blood count was within normal limits and no eosinophilia was present. The urinalysis showed a specific gravity of 1.022, 30-35 WBC/HPF, and a trace of protein. Sediment was loaded with bacteria. Two urine cultures grew out more than 100,000 colonies per ml. of gamma and alpha streptococci. Hepatic tests are summarized in Fig. 1.

Because of her unexplained symptomatology and laboratory evidence pointing to hepatic dysfunction, a liver biopsy was performed on the 12th hospital day and revealed multiple non-caseating granulomas (Fig. 2). There was no evidence in the biopsy of cholestasis or hepatocellular injury. Special stains were negative for acid-fast bacilli. Liver biopsy

Date	3/28	4/4
BILIRUBIN		
Total	4.0	0.7
Direct	2.2	0.2
ALKALINE PHOSPHATASE (B.L. units normal 2.5)	1.9	3.0
SGOT (Karmen units)	154	61
ICD (W-WA units)	510	210

Fig. 1.—Hepatic tests of this patient during her first admission in 1966. These tests were all normal at the time of her second admission.

culture for tubercule bacilli was negative.

A tuberculin skin test (second strength PPD) was positive with two-centimeter nodular induration. Skin tests for histoplasmosis, coccidioidomycosis and blastonycosis were negative. The serum calcium was 9.6 and the serum phosphorus was 3.6 mg. per 100 ml. X-ray examinations of the chest, gall bladder, urinary tract, and upper gastrointestinal tract were normal. Several gastric washings, sputum and urine cultures for acid-fast bacillus were repeatedly negative. Stools were negative for ova, parasites, and occult blood. Virus cultures of the stool in tissue culture and suckling mice were negative. The serum electrophoresis revealed a reversed ratio of 3.7 gms. albumin to 4.3 gms. globulin per 100 ml. The value for gamma globulin was 2.1 gm. per 100 ml. The serum immunoelectrophoresis was normal.

Because the search for a specific etiology of the granulomatous liver disease was unrevealing, the patient was discharged with the diagnosis of probable sarcoidosis. No specific treatment was prescribed.

During her subsequent periodic visits to the out-patient clinic the patient occasionally complained of left flank pain. Except for this she was well. She was not treated at any time with hormonal or antibacterial agents.

She was readmitted to Presbyterian-St. Luke's Hospital in August of 1967 for a second liver biopsy. The patient was without symptoms and her physical examination was normal. Her hepatic tests were entirely within normal limits. She also had a normal blood count, urinalysis, blood urea nitrogen, two-hour post-

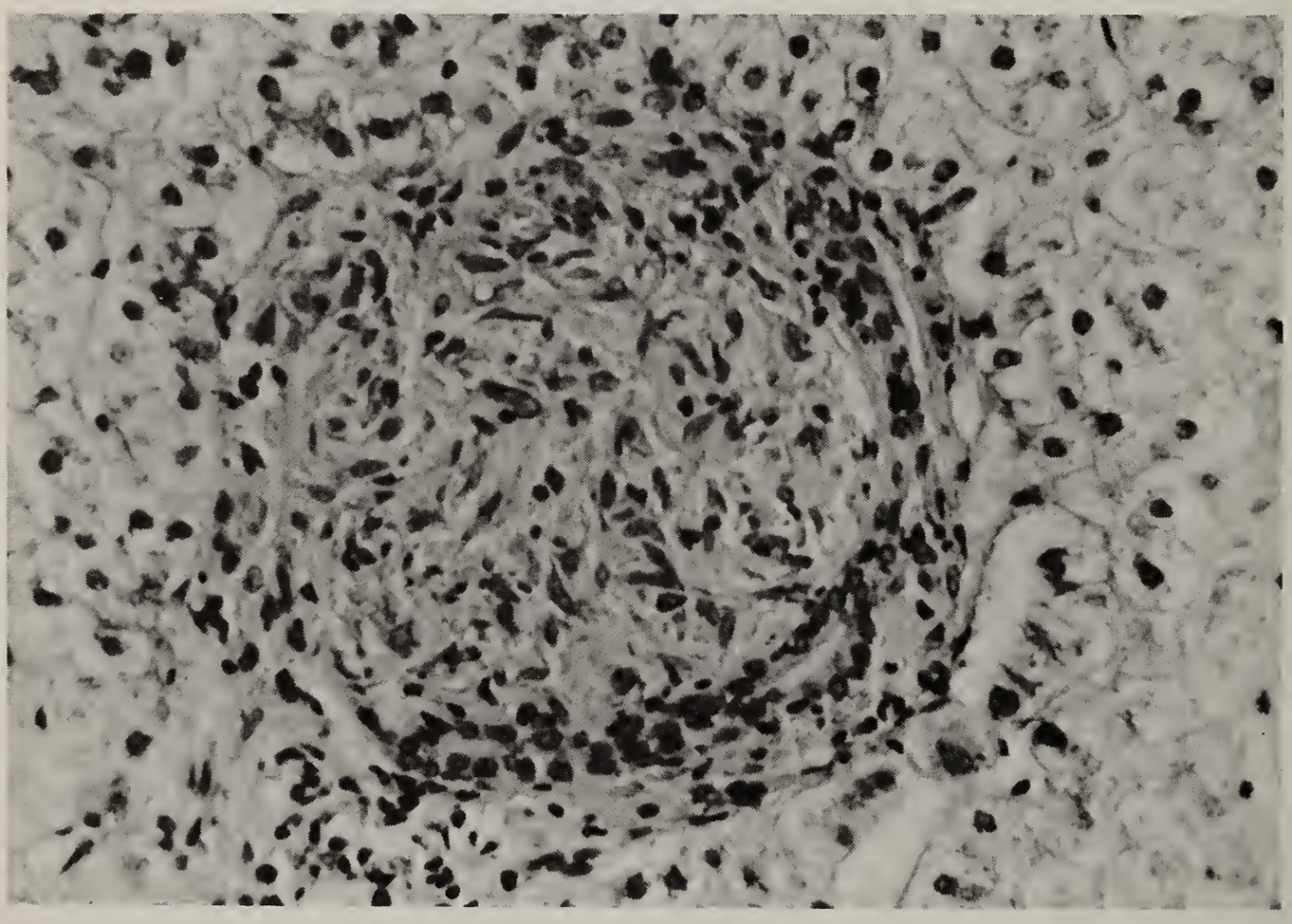

Fig. 2.—Hematoxylin-eosin stained section of the patient's *first* liver biopsy showing a well demarcated granuloma (original magnification 370X).

prandial blood sugar, serum calcium and phosphorous. There was 4% retention of bromsulphalein at 45 minutes. Three six-hour urine collections for acid-fast bacilli were negative. Radiographs of her chest, hands, and kidneys were within normal limits. Liver biopsy was normal. There was no evidence of granuloma.

DISCUSSION

The occurrence of granulomas in the liver following sulfonamide ingestion was described twenty-five years ago. More, McMillan, and Duff[1] found in a post mortem study that 5.9% of 375 patients who had taken sulfonamides had granulomatous disease somewhere in the body, and 2.1% of these patients had hepatic granulomas. Maisel, *et al.*,[2] found that parenterally administered sulfadiazine caused granulomas in the myocardiums and kidneys of dogs after 14 days. A number of authors have reviewed the problem of hepatic granulomatous disease in recent years[3] but, with one exception, sulfonamides have not been listed as possible causes.[4] To our knowledge there has been only one report of liver granulomas following the ingestion of any of the newer sulfonamides.[5] There have been, however, clearly documented cases of other forms of hepatotoxicity apparently due to these agents.[6]

There has been considerable interest, particularly in the past two decades, in the role of drugs in the production of liver injury. Although cholestasis and hepatocellular injury are well recognized forms of sulfonamide hepatotoxicity, granulomas of the liver have not been mentioned in the general or specific literature on drug-induced liver injury.

Our patient had had two previous episodes of sulfonamide allergy prior to her first admission. She was given sulfisoxazole and developed another overt allergic reaction, this time with jaundice. A liver biopsy was done, and hepatic granulomas were found. Because study of the patient failed to show an obvious cause for the granulomatous disease, it was assumed that she had sarcoidosis. Her subsequent good health without treatment, which was felt to be inconsistent with active sarcoidosis, prompted further study. At that time all laboratory tests were found to be normal and liver biopsy was also normal. It is, of course, possible that she still has granulomas in her liver and that the second biopsy failed to sample an involved area. However, in view of her course and her obvious good health at this time, we feel it is more likely that she is indeed normal now.

Sulfisoxazole is a common and widely used drug. Its toxic effects have been manifested by hypersensitivity and toxic reactions of the blood, liver, kidney, lungs, joints, gastrointestinal tract, and skin. That the liver may react to sulfonamides with granuloma formation is not new, as the phenomenon has been seen in the past on post mortem examination and reported more recently with the sulfonamide compounds[7] used for treatment of diabetes. This case is presented to illustrate the importance of eliciting a careful history of drug allergy and also to underscore the necessity of seeking out toxic or allergic causes of hepatic granulomas before making a presumptive diagnosis of a chronic disease which often commits the patient to a course of unnecessary and protracted treatment.

SUMMARY

A jaundiced patient whose liver biopsy revealed multiple noncaseating granulomas is presented.

Because of lack of evidence of any of the specific diseases which usually cause hepatic granulomas, the patient was discharged with the diagnosis of sarcoidosis. In retrospect it was realized that the patient had a known sulfonamide allergy and that her symptoms exacerbated when she was given sulfisoxazole in the hospital. Because of excellent subsequent health the patient was studied and biopsied again one year later with normal biochemical and histological findings.

It is stressed that whenever hepatic granulomas are found, and no specific etiology is apparent, drug allergy should be considered in the differential diagnosis.

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RECENT ADVANCES IN THE PHARMACOLOGY OF PARKINSON'S DISEASE

Harold L. Klawans, Jr.*

By the early sixties, pharmacologists had been able to demonstrate that nearly all the drugs which were useful in the treatment of parkinsonism possessed significant central anticholinergic properties.[1] It was believed that the central acetylcholine inhibition of these agents resulted in their clinical usefulness. This reasoning led to the supposition of some sort of increased activity of acetylcholine in the parkinsonian patient. The basis of this increased activity was unknown but its successful antagonism by a wide variety of agents was well accepted. The notion of central acetylcholine antagonism as the mechanism of action was applied not only to belladonna alkaloids and the synthetic alkaloids such as trihexyphenidyl (Artane) but also for the various phenothiazines and antihistamines which were used in the therapy of parkinsonism. The sole major exception to this rule was dextroamphetamine. One of the major values of this agent was in reducing oculogyric crises and since these were no longer being seen, no one worried very much about this exception.

The last ten years, on the other hand, have brought about a large number of advances which have resulted in significant alterations in the theory of the pharmacology of parkinsonism. The first major breakthrough was the emergence of drug-induced parkinsonism. A generation of physiologists had been unable to produce parkinsonism in experimental animals despite thousands of painstakingly placed stereotactic lesions. Now it was possible to elicit such symptoms with a variety of agents. The most noteworthy of these were reserpine and many phenothiazines. Of the latter, chlorpromazine was the most widely used and the best studied. The sole mechanism of action of reserpine is to cause depletion of a variety of stored biogenic amines including serotonin and catecholamines. Of the variety of actions which are characteristic of phenothiazines none appeared to result in an increased effect of acetylcholine in the central nervous system. Standard antiparkinsonism agents were able to overcome the drug-induced syndromes quite easily.

Independent of these discoveries, a great deal of attention has been given to dopamine in the last 10 years. Dopamine is the simplest of the three catecholamines and is known to be a precursor of the other two catecholamines; norepinephrine and epinephrine. The finding that about one-half of the total brain catecholamine was dopamine did not support the notion that the sole function of this amine was that of norepinephrine precursor. It was later found that in some

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areas of the brain, notably the striatum (caudate and putamen) there is about 100 times as much dopamine as norepinephrine and that the turnover of dopamine is faster than that of norepinephrine. These results strongly suggest a role for dopamine independent of its role as norepinephrine precursor.[7]

The development of a histochemical, fluorescent technique for the demonstration of serotonin and catecholamines within tissue slices made it possible to discover the exact cellular localization of these amines.[2] Specific collections of neuronal cell bodies rich in either serotonin or catecholamine were found throughout the brain stem. It was shown that in the striatum the dopamine was not in the striatal neurons but in a fine meshwork of small nerve endings. The cell bodies of these neurons are located in the substantia nigra. Destruction of the substantia nigra results in loss of dopamine from the ipsilateral striatum.[8] Certain brain stem lesions which interrupt the proposed path of the axons from the substantia nigra to the striatum result in dopamine loss in both areas along with neuronal degeneration in the substantia nigra.[2] The nerve endings in the striatum are too small to be seen by standard microscopic techniques so that the dopamine-depleted striatum appears histologically to be normal. These studies have resulted in the suggestion of a new neuronal pathway which was hitherto unsuspected. This has been named the nigrostriatal pathway since the cell bodies are in the substantia nigra of the midbrain and the terminations are in the striatum. These neurons contain dopamine.

If an electrode is placed in the substantia nigra and pulses are passed through it, dopamine is released in the striatum. It has been proposed that dopamine is in fact the transmitter of the nigrostriatal neurons. If this is so, what is the effect of this transmitter? It appears that at most synapses from molluscs to mammals dopamine results in an inhibitory effect of the receptor site. Inhibition also appears to be caused by application of dopamine to striatal neurons.[7]

What is the connection between such an inhibitory "dopaminergic" pathway and Parkinson's disease? In Parkinson's disease the most consistent neuropathologic change is degeneration of the neurons of the substantia nigra. This is true in both idiopathic and postencephalitic parkinsonism. If this is the case then one would expect that there would be loss of dopamine in the striatum in these patients. This has been found to be true in all cases in which this has been measured.

The next problem then is to reconcile the loss of dopamine inhibition with clinical usefulness of anticholinergic agents. This has been done by demonstrating that acetylcholine and dopamine have antagonistic effects on the neurons of the striatum with acetylcholine being facilitory and dopamine inhibitory. These two systems are present in normal individuals. The striatum in fact has the highest concentrations of both acetylcholine and dopamine of the entire brain. One system is injured in parkinsonism while the other is intact. This could well result in an imbalance of input to the striatal neurons. If one were to antagonize the remaining normal system, normal balance could be restored. It is now felt that central anticholigenic medications are antagonizing a normal system in Parkinson patients.[3,5] This is a change more in theory than in practice. The same drugs are now used, not to combat an abnormal effect of acetylcholine, but to depress the normal effect of acetylcholine on cells whose normal antagonistic input has been lost. It should be noted that in patients with parkinsonism, although dopamine is lost from the striatum, acetylcholine is not.

This theory of neurotransmitted imbalance cannot only explain the effectiveness of the various anticholinergic agents but it can also explain the effectiveness of dextroamphetamine. This catecholamine analogue has been shown to act directly on dopamine receptors in the brain.[9] In this case then imbalance is restored by replacing the missing transmitter of the dopamine system.

Drug-induced parkinsonism is also

consistent with the idea that acetylcholine dopamine imbalance is the basis of such symptoms. Reserpine depletes the brain of dopamine while chlorpromazine is a competitive inhibitor of dopamine. Both of these actions would swing the balance in favor of acetylcholine. The anticholinergic actions of standard medications would restore the balance.

The worth of a theory, however, rests in its ability to bring about new ideas, not in the ease with which it explains old observations.

The value of this theory rests now on a newer form of therapy, L-Dopa or L-3,4 dihydroxyphenylalanine. This is the immediate precursor of dopamine. Dopamine is formed from it by decarboxylation. L-Dopa can cross the blood-brain barrier, whereas dopamine itself cannot. Furthermore, the enzyme which catalyzes the decarboxylation of L-Dopa to dopamine is not decreased in the brain of parkinsonian patients. If, then, this dopamine precursor can get into the brain and be decarboxylated to dopamine in patients with Parkinson's disease, the signs and symptoms of parkinsonism should be reduced by this agent. This has been tried and it appears that such therapy is beneficial.[4,10]

The most exciting work in the treatment of these problems revolves around the use of L-Dopa. The experimental trials have shown that this agent is very effective, especially in reducing akinesia. This does not mean that L-Dopa restores physiologic balance. L-Dopa appears to cause peculiar, uncomfortable and distorting movements of the face and tongue in many patients who receive large enough doses to help their parkinsonism. The L-Dopa approach then is to attack the imbalance not by assaulting the normal system but by building up the defective system.

It also appears that the suggestion of a dopamine acetylcholine antagonism is a definite oversimplification, since two other possible transmitters, serotonin and histamine, may be involved in the normal balance of the striatum.[3,6] It is known also that in Parkinson's disease the striatal levels of serotonin are depressed. Although the theory of dopamine-acetylcholine imbalance has obvious limitations, it has led to a more complete understanding of the pharmacology of drugs which either cause or relieve parkinsonism.

SUMMARY

The pharmacology of a number of drugs which cause or relieve parkinsonism in man is reviewed and presented in relationship to the recently demonstrated nigrostriatal dopaminergic pathway. An acetylcholine-dopamine antagonism is proposed as a natural state in the striatum. It is suggested that factors which disrupt the normal balance in favor of acetylcholine result in parkinsonism while factors which tend to restore the balance relieve parkinsonism.

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BOOK REVIEW

AN ATLAS OF ADVANCED SURGICAL TECHNIQUES by Edward J. Beattie and Steven G. Economou. Illustrated by Jo Ann Goldin. Atlas, Cloth, 422 pp., illustrated. Philadelphia: W. B. Saunders, 1968. $20.00.*

The term "atlas" was probably derived from the title of a cartographical work of Gerhardus Mercator published in 1595. The title pages of this and other similar volumes of the 16th Century often displayed a representation of Atlas bearing the heavens. Today an atlas refers to any bound collection of tables, charts or plates illustrating a specific subject. Such is the format of the new volume, *An Atlas of Advanced Surgical Techniques*. Although a number of good atlases illustrating basic surgical techniques are currently available, none is devoted exclusively to depicting the advanced or complex operation. To fulfill this need, *An Atlas of Advanced Surgical Techniques* has been written.

Thirty-one selected operations are described. Although the selection of operations might seem arbitrary, they are all procedures for which a well-trained senior resident or general surgeon should be qualified and which he might be required to perform. This atlas, therefore, should not be regarded as a specialty treatise. Thirteen procedures are devoted to the abdomen, seven to the head and neck and thorax, while the remainder involve operations on the extremities or the integumentary system. A panel of eleven experienced surgeons have collaborated with the authors by contributing various chapters.

A brief text supported by a few bibliographic references introduces each operation, often outlining the indications, diagnosis and principles of treatment with anticipated results. The lack of a uniform style, however, is apparent and might be criticized. Nevertheless, the variations of each author's introduction are informative, worthwhile, and appeal to the reader's interest.

The success of any atlas is predicated chiefly upon the fidelity of its illustrations. The art work is superb. Ink-wash drawings have been used throughout except where it was essential to focus accurately on technical detail. Here, crisp line drawings are used to define relationships such as occult neurovascular structures to contiguous organs in various regions as the mediastinum, hilum of the lung, adrenal gland, the axilla and groin. Short descriptive paragraphs, sequentially lettered, appear on the facing page. When the text on a subsequent page requires a second reference to a drawing, the latter is repeated, thus eliminating the disconcerting necessity of turning back the page. The artistic grouping of several figures on a page conserves the reader's time. The minimal use of labels avoids clutter and accentuates the drawings.

The authors presume that the surgeon who refers to this atlas already has mastered the basic principles of surgical technique. It is for this well-trained general surgeon that the book will have its greatest attraction.

FREDERIC A. DEPEYSTER

**EDITOR'S NOTE: Edward J. Beattie, formerly Chairman of the Division of Surgery, is now Chairman of Surgery, Memorial Hospital for Cancer and Allied Diseases, New York City. Steven G. Economou is Attending Surgeon, Presbyterian-St. Luke's Hospital, and Professor of Clinical Surgery, University of Illinois.*

ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Myers, Kenneth A., Paul, Harold A., and Julian, Ormand C.: Response to Isoproterenol and THAM During Hemorrhagic Shock. *Surgery, 64:653-660, Sept. 1968.*

Dogs were studied during hemorrhagic shock produced by the Lillehei apparatus which permitted bleeding to a predetermined mean arterial pressure. Arterial and portal venous pressures were produced through a gated sine wave electromagnetic flow meter. Arterial (superior mesenteric) and portal venous blood samples were taken at 20-minute intervals for hemoglobin, hematocrit, oxygen tension (polarographic analysis) and pH with base excess or deficit (Astrup technic).

Oxygen saturation was then calculated from oxygen tension and the nomogram of Rossing & Cain. Oxygen consumption of the splanchnic viscera was determined by the Fick principle.

Portal blood flow, intestinal oxygen consumption, and total oxygen consumption were studied in comparison to a group in which metabolic acidosis was controlled with THAM. Response to short infusion of isoproterenol given at intervals was compared. Decrease of portal blood flow and intestinal oxygen consumption occurred in both groups during shock. A marked initial increase in intestinal oxygen consumption occurred in THAM-treated dogs right after retransfusion. This did not happen in control animals. Total oxygen consumption was greater with the THAM group both during and after shock. Isoproterenol caused significant increases in portal flow and intestinal oxygen consumption before shock began. Response to isoproterenol was greatly reduced during shock and after retransfusion.

Correction of metabolic acidosis with THAM did not improve response to isoproterenol.

Dold, H. J. and Northrop, R. L. (Introduced by Friedrich Deinhardt): The Nonspecific Inhibitors of Rubella-Virus Hemagglutination. *Proc. Soc. Exp. Biol. Med., 128:577-581, 1968.*

The nonspecific inhibitor(s) of rubella-virus hemagglutination were removed from human serum by the rapid, simple, and specific procedure of adding manganous chloride and heparin to the serum. This procedure was shown to precipitate preferentially β-lipoprotein without altering the immunoglobulin level in serum. The rubella-virus HI antibody titers after M-H treatment were equal to, or greater than, that after kaolin absorption and correlated in a high degree of neutralizing antibody titers.

Holinger, Paul H.: Benign Tumors of the Trachea and Bronchi. *Otolaryng. Clin. N. Amer., 1:219-238, June 1968.*

Benign tumors of the trachea and bronchi are divided into inflammatory and neoplastic growths. Granulomas, polyps, and amyloid deposits constitute the nonspecific tumors while tuberculomas, Boeck's sarcoid, syphilitic granulomas, scleroma, and the fungus forms of actinomycosis and histoplasmosis constitute the specific granulomas. Benign neoplasms can be divided into epithelial tumors: the papillomas and adenomas, and mesodermal tumors: hemangioma, fibroma, lipoma, chondroma, osteoma, tracheopathia osteoplastica, and the myomas. Hamartomas are classified as tumors of developmental origin.

The symptoms are usually of long duration and are those associated with the bronchial obstruction they produce. The severity of symptoms increases as the site of origin rises in the bronchi or trachea. Cough, more or less productive depending on the degree of associated suppuration, is the earliest and most constant symptom. Wheezing may be an early symptom increasing to dyspnea or even asphyxia dependent on the location of the tumor. The severity of the respiratory obstruction increases if a segment, lobe, lung, or the trachea itself is involved. Hemoptysis is not so constant a symptom as it is in malignant neoplasms except for adenomas and tracheopathia osteoplastica in which hemoptysis is a characteristic symptom. Otherwise hemoptysis is associated with the pulmonary suppuration rather than with the tumor itself.

The diagnosis is suspected when physical and roentgenographic examinations show the characteristic findings of lower respiratory tract obstruction or a "silent" tumor. Fluoroscopic studies, posteroanterior and lateral films, inspiratory and expiratory comparisons, and laminography are all important. A negative chest survey x-ray may result if the tumor is tracheal, but invariably an asthmatic wheeze is present that should lead to further study. Bronchoscopy is the most common means of obtaining tissue for histologic confirmation of the diagnosis.

The therapy is dependent primarily on the degree of associated suppuration and lung destruction distal to the tumor and only secondarily on the histologic nature of the tumor. Bronchoscopic removal of the obstructing mass is done by forceps, snare, resectoscope, or coring of the lumen with the bronchoscope itself. Surgical procedures consist of bronchotomy, sleeve resections, or segmental, lobar, or total lung resections, again determined by the location of the tumor, its duration, and peripheral lung changes. Surgery is generally more conservative than that used for bronchogenic malignant tumors.

Ing, T. S., Anderson, R. N., Passovoy, M., and Lucis, O. J.: Dose-Response Relationship in Angiotensin Bioassay. *Cardiov. Res. 2:39-42, Jan. 1968.*

The dose-response relationship of synthetic valine-5-angiotensin II, aspartic β-amide at the dose levels commonly employed in the estimation of renin activity of blood—namely between 1 and 6 ng—was determined in albino rats. The data were analysed statistically. It was shown that it was preferable to use the logarithmic transformation of the dose in the bioassay.

Wallner, L. J., Hill, B. J., Waldrop, W., and Monroe, C.: Voice Changes Following Adenotonsillectomy. A Study of Velar Function by Cinefluorography and Video Tape. *Laryngoscope, 78:1410-1418, Aug. 1968.*

Alteration of the voice is a common occurrence after adenotonsillectomy and was observed in 26 of 29 patients in a prospective study herein reported. These alterations are usually transitory and self-limited, with actual improvement in speech as the final result.

Severe deterioration of the voice occasionally follows surgery. The chief factors seem to be adenoidectomy resulting in inadequate velar closure, scarring of the pillars, short palate, roomy nasopharynx, or some combination of these.

Cinefluorography with simultaneous video tape proved valuable in investigating velar function. Its use can help determine which patient may develop serious voice defects after surgery, or assist in therapy when this has occurred. It is not a practical method for routine preoperative use.

Caution should be used in deciding on adenoidectomy in patients with repaired cleft palate, and submucous cleft and bifid uvula.

The treatment of voice alterations after adenotonsillectomy is expectant for the first few weeks. If the abnormality persists or worsens, cinefluorography and speech therapy are indicated. If speech therapy does not restore an acceptable voice, surgery may be considered and either Teflon injection or pharyngeal flaps are possibilities.

The doctrine of informed consent raises the question as to whether the possibility of voice changes after surgery should be discussed with the parents preoperatively.

Northrop, G.: Effect of Adrenergic Blocking Agents on Epinephrine- and 3′, 5′-AMP-induced Responses in the Perfused Rat Liver. *J. Pharmacol. Exp. Ther., 159:22-28, 1968.*

The relationship of glucose and cation fluxes following epinephrine administration has been studied extensively in recent years. In the present study the isolated perfused rat liver was employed. This technique permitted intraportal infusions of epinephrine or the cyclic nucleotide, 3′, 5′-AMP, with and without previous treatment with the *alpha-* and *beta-*adrenergic blocking agents, dihydroergotamine and dichloroisoproterenol, followed by the subsequent measurement of blood flow rate and blood-glucose and blood-potassium concentrations in the hepatic efferent fluid. Epinephrine and 3′, 5′-AMP caused hyperglycemia and hypokalemia. Pretreatment with dihydroergotamine prevented these metabolic responses, and pretreatment with dichloroisoproterenol prevented epinephrine-induced metabolic changes; however, this agent was without effect on the cyclic nucleotide-induced responses. Epinephrine-induced vaso-constriction was blocked by pretreatment with dihydroergotamine but not by dichloroisoproterenol. After infusion of 3′, 5′-AMP there was no demonstrable change in rate of blood flow.

Garron, D. C. and Cheifetz, D. I.: Electroshock Therapy and Bender-Gestalt Performance. *Percep. Motor Skills, 26:9-10, 1968.*

Impaired copying of the Bender Visual-Motor Gestalt (BG) designs is often regarded as diagnostic of brain damage. Question has been raised whether such impaired copying, in patients who have had EST recently, should be attributed to the effects of EST. Pre- and post-EST BG's from 19 psychiatric patients were compared with repeated BG's from control patients. No differences between the groups appeared before or after EST. No patient in either group did appreciably worse on BG_2 than on BG_1. Post-EST patients were tested a few days after administration of the last EST in a series. We conclude that the usual diagnostic inferences may be made from impaired copying a few days after EST.

Leavitt, F.: EEG Activation and Reaction Time. *J. Exp. Psychol. 77:194-199, 1968.*

Reaction time studies with normal subjects have yielded results in support of the relationship between EEG activation and behavioral arousal. Speed of response has been employed as the behavioral index of arousal with the following results: Fast response with low voltage, fast EEG activity and slow response with high voltage, slow EEG activity. A major shortcoming in these studies has been the failure to consider foreperiod duration as an important determinant of speed of response when ample evidence exists for a relationship between reaction time and foreperiod. To clarify this matter, the covariation of reaction time and alpha desynchronization was investigated at foreperiods of 200, 500, 1500, and 4,000 msec. The results demonstrated that reaction time and alpha desynchronization are significantly influenced by variations in the foreperiod condition. Reliably faster RT and maximal alpha desynchronization occurred 500 msec. after the warning signal; however, within the context of the foreperiod, the two variables did not covary. A unitary underlying arousal process was rejected in favor of multiple neural arousal processes.

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Cartilage Lysozyme

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Family Planning Service

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VOL. 7. NO. 4 OCTOBER 1968

TABLE OF CONTENTS

page

130 . . . . . **Studies on Cartilage Lysozyme**
KLAUS E. KUETTNER and REUBEN EISENSTEIN

136 . . . . . **Aggregated Micelles: Possible Role in Gas Transference**
BERNARD ECANOW, REUBEN BALAGOT, and WALTER STANASZEK

139 . . . . . **A Computerized Hospital: How? What? Why? When?**
JULIA T. APTER

147 . . . . . **The Family Planning Service**
ARTHUR H. KLAWANS and JOYCE C. MAYER

150 . . . . . **Abstracts**

STUDIES ON CARTILAGE LYSOZYME

Klaus E. Kuettner and Reuben Eisenstein

Over 40 years ago Sir Alexander Fleming, while searching for antibacterial substances, discovered an enzyme in the egg white of birds which had a striking ability to lyse bacterial cells and was therefore given the name lysozyme. For some time he entertained the thought that the antibiotic properties of lysozyme could be used in clinical medicine. Unfortunately, it was not effective against most pathogenic bacteria, and his research turned to other antibacterial substances, culminating in the discovery of penicillin. Since Fleming's original observation, lysozyme has been rather extensively investigated, primarily from the physical and chemical points of view. It is a basic low molecular weight protein which specifically splits the link between N-acetylmuramic acid and β-N-acetyl glucosamine, a linkage present only in bacterial cell wall substances. Thus, there is no known substrate for this enzyme in animal tissues and its biological function in such tissues remains completely unknown. It is, however, present in many mammalian tissues and body fluids, with the highest concentration being found in cartilage. Some acidic macromolecules isolated from cartilage, such as the mucoproteins and the chondroitin sulfates, combine with it to form an insoluble but dissociable complex under specific ionic conditions.

Our own interest in this material became aroused when one of us (KEK) found in cartilage a substance with all the biological and physiochemical properties of lysozyme.[1] The highest concentrations were found in that portion of epiphyseal cartilage undergoing rapid transformation into bone, as compared with the levels in cartilage more distant from the cartilage-bone junction; in newly formed bone; and in cartilage which is not destined to ossify, such as that of the nasal septum. Another pertinent observation was that lysozyme was found to be present in much higher concentration in the cartilage of young growing animals than in that of older, more slowly growing animals. These observations seemed particularly intriguing since Wolinsky and Cohn[2] had shown that in bone the concentration of lysozyme diminished after large amounts of parathyroid extract were injected into rabbits. Schumacher[3] has also noted that lysozyme is present in high concentration in human cervical mucus and that its concentration decreases during the estrogenic phase of the menstrual cycle.

Following these initial observations we hypothesized that lysozyme might have some function in cartilage which is related either to cartilage transformation or

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calcification. This hypothesis was based in part on our data and in part on the general biological principle that it is unlikely that any material is present in high concentration in living tissues without having some function, unless it is a waste product which is to be disposed.

As a preliminary approach to this problem, we applied a few simple procedures commonly used to study materials without known physiological functions. One of these was to study the effects of adding lysozyme to living tissues. We chose to do this in organ culture, where isolated cartilage could be studied without the interference of general body metabolism. The results in cartilage (derived either from puppies or embryos of mice, humans, or chicks) were morphologically dramatic.[4] Effects were observed only in cartilage containing an epiphyseal plate and destined to be transformed into bone, but not in nonossifying cartilage such as that of the nasal septum, the ear, or the trachea. Grossly, there was a striking opacification of the cartilaginous portion of the tissue exposed to high concentrations of lysozyme. The distribution of the opacification region was remarkable in that it spared the epiphyseal growth zone, precisely in the area of the highest lysozyme concentration. Histologically, there were also striking alterations in the staining properties of the cartilage, particularly marked by increased acidophilia of the matrix (Fig. 1). These changes were less extensive in those parts of the epiphysis in which lysozyme is normally present in highest concentration. The above effects were not produced by the addition of other proteins of nearly neutral isoelectric point, such as egg albumin and bovine chondromucoprotein.

As an additional control, protamine, a nucleoprotein derived from salmon sperm, was used. Protamine is, like lysozyme, an extremely basic protein and a heparin antagonist. However, unlike lysozyme, it has no enzymatic activity. The addition of protamine to organ cultures induced gross and histologic changes which were superficially similar to those induced by lysozyme, that is, gross opacification of the explants and similar histologic alterations in the tissue. However, unlike lysozyme, it also induced darkening and diffuse histologic alterations in the epiphyseal growth zone, as well as inhibition of cartilage growth characterized by a rather striking hypertrophy and perhaps hyperplasia of the chondrocytes (Fig. 2). In comparison, lysozyme did not appear to alter the viability of the organ culture no matter how high a concentration was used.

Another difference noted between the effects of lysozyme and protamine was that when the tissue culture medium, containing lysozyme, was replaced with lysozyme-free medium, all the gross and histologic changes rapidly reverted to normal; when done with protamine this reversal did not occur.

In order for the changes induced by lysozyme to occur, the cartilage has to be viable. Thus, in cartilage devitalized by freezing and thawing or by the addition of KCN, lysozyme had no effect. Semi-quantitative measurements have indicated that both living and dead cartilage absorb large amounts of added lysozyme from the tissue culture medium. However, living cultures absorb more than dead ones.

We do not yet understand the significance of the changes in the staining characteristics of lysozyme-treated cartilage. These changes are characterized by a diffuse eosinophilia of the cartilage matrix, except in the zone of columnar cells of the cartilage, where eosinophilia is restricted to a capsule-like ring of dense eosinophilic material around the chondrocytes in the columns (Fig. 3). This material is stained red by the PAS technique and with Gomori's trichrome stain. It is not metachromatic, so it probably does not contain significant amounts of acid mucopolysaccharides. It is reasonable to suggest that this material is either 1) lysozyme; 2) lysozyme which has been altered by chondrocytes; or 3) the product of some type of interaction between lysozyme and the matrix of cartilage.

To test whether the lysozyme effect in

Fig. 1.—Mouse embryonic femur cultured in medium containing 1 mg/ml of egg white lysozyme. Eosinophilic deposits form capsules around chondrocytes and there are punctate deposits of similar material in the intervening matrix. The chondrocytes appear normal. Hematoxylin-eosin stain, approx. 500X.

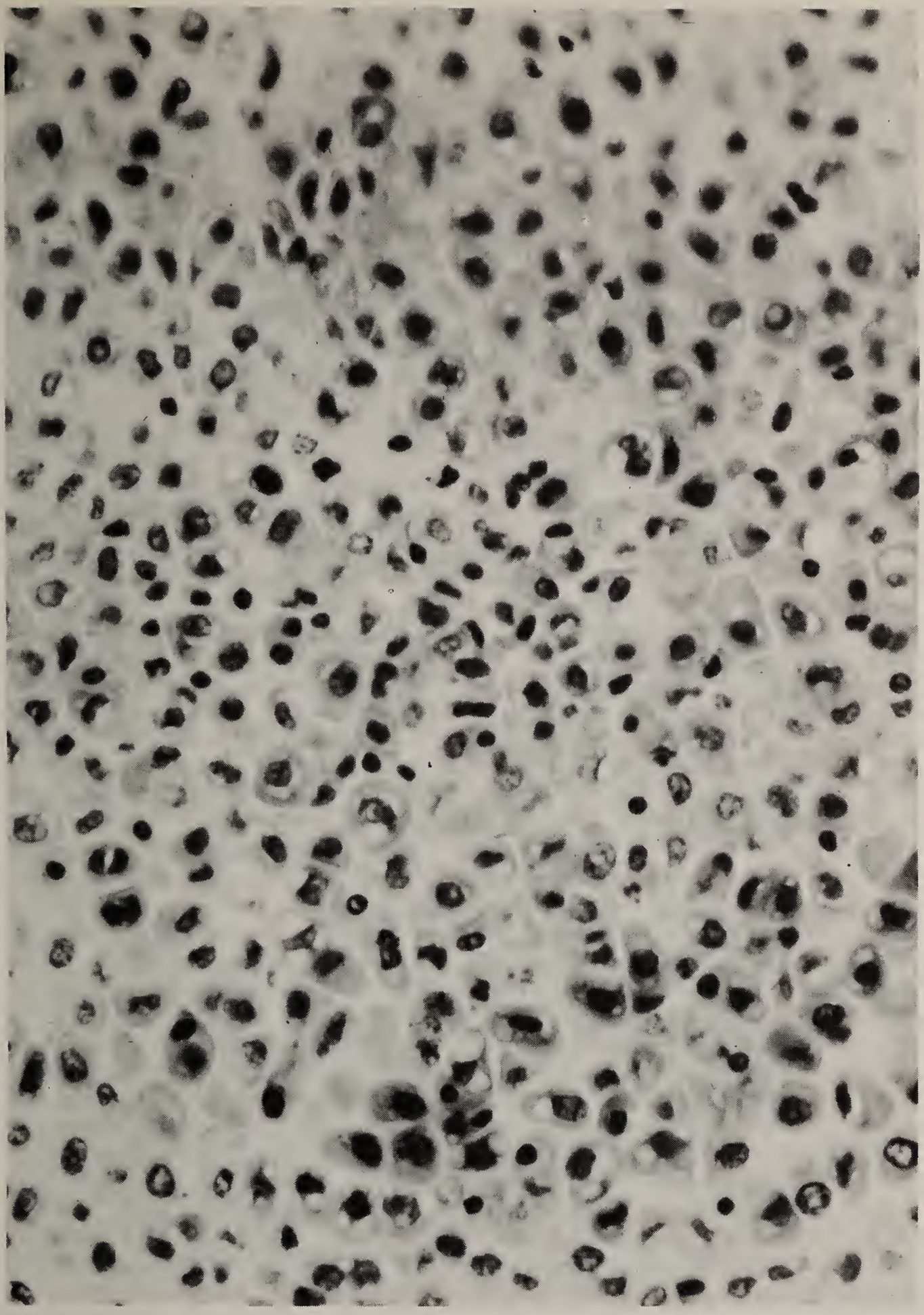

Fig. 2.—Mouse embryonic femur cultured in medium containing 1 mg/ml of salmon sperm protamine. Eosinophilic deposits are present in the stroma as when lysozyme is used. There is also crowding of chondrocytes with large, darkly stained nuclei some in mitosis. Since the explant did not grow, the cellular crowding is considered to represent an arrest of matrix synthesis. Hematoxylin-eosin stain, 500X.

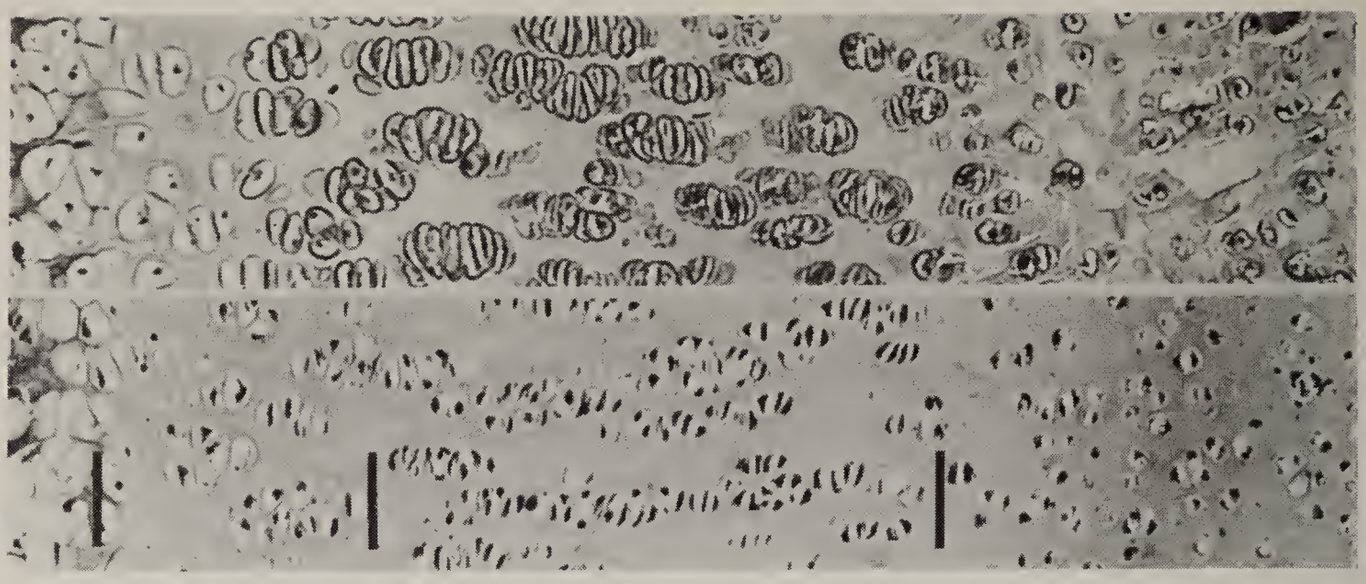

Fig. 3.—Puppy scapula cultured in medium containing 1 mg/ml lysozyme. Densely eosinophilic deposits surround chondrocytes, but only in the columnar zones of the cartilage. A control specimen is pictured beneath for comparison. Hematoxylin-eosin stain, 100X.

organ culture was due to its enzymatic activity, two experiments were performed. In the first, puppy cartilage was incubated for up to five hours in high concentrations of lysozyme. There was no apparent digestion of any of the components of the cartilage matrix, at least by histochemical tests. Secondly, ultraviolet light was used to irradiate a solution of lysozyme in order to alter the tertiary structure of the molecule without significantly affecting the amino acid sequence or composition. This procedure resulted in an inactivation of the enzymatic activity of lysozyme as tested with the specific substrate, *Micrococcus lysodeikticus*. Addition of this inactivated lysozyme to cartilage induced changes which were quite different histologically from those induced by the addition of intact lysozyme. Material with similar staining properties was present within the cartilage, but it was now seen exclusively within chondrocytes as punctate eosinophilic deposits. There was no detectable change in the matrix. The most likely interpretation of this histologic finding is that the eosinophilic cytoplasmic droplets represent ingested, perhaps altered, lysozyme which was stored within the chondrocytes.

One of the problems we faced at this point was that the lysozyme we had used was from chicken egg white, a source easily available commercially in very high purity. Unfortunately, bird lysozyme is immunologically different from those mammalian lysozymes which have been studied. Interpretation of changes induced by the addition of such lysozyme to cultures of mammalian tissue is therefore subject to question. However, we have recently found that changes similar to those noted in mammalian tissues could also be induced in organ cultures of chick embryos.[5]

During our study of chick embryos we noted that not all cartilage responded to lysozyme in culture. When this was studied in greater detail, it was found that femurs of very young embryos (approximately eight days old) did not change morphologically when lysozyme was added to the culture medium. However, older embryos (12 or more days old) showed the characteristic histologic response to lysozyme. The femurs of eight-day old chick embryos have not yet developed the cartilaginous epiphysis which is present in older embryos. This indicates that lysozyme may be involved in a rather precise biochemical control

mechanism in the development of bone. Support of this idea is also obtained from semi-quantitative biochemical data indicating that lysozyme is present in much higher concentration in cartilage of chick embryo limbs after the epiphyseal plate has formed than before this stage. There seems to be a specific time in the development of the embryo at which lysozyme begins to appear in high concentration. At the same time, but not before, addition of lysozyme to embryonic tissue in culture results in a characteristic type of morphologic response. The formation of a specific organ within the cartilage, the cartilaginous epiphysis, is associated with this biochemical event and controls the subsequent morphologic responses seen in organ culture.

SUMMARY

It must be emphasized that we have no real evidence regarding the function of lysozyme *in vivo*. However, it would appear to be an unlikely biological accident that it is present in such high concentration in a specific anatomic zone of cartilage; that its concentration is altered in response to materials known to affect cartilage and bone metabolism, such as parathyroid hormone; that it appears at a specific time in embryogenesis; and that it can induce rather specific morphologic changes in cartilage *in vitro*, and only in preosseous cartilage. We do not yet know whether such a function is related to some unknown enzymatic activity or to its properties as one of the few basic proteins of living tissues.

ACKNOWLEDGMENTS

We wish to thank Dr. Robert D. Ray and Dr. G. M. Hass without whose constant encouragement this work would never have progressed. This work would not have been possible without the active participation by Mr. Lawrence Soble, M.S., and Mr. Richard Croxen who planned and carried out much of the organ culture work, and Mr. Harald Guenther who performed the biochemical estimations and isolations. Thanks are also due to Miss Alice Laurick for her skillful technical assistance and to Mr. Michael Haklin for his cooperation in obtaining suitable specimens for the organ culture work. The critical reading of the manuscript by Dr. Arthur Lindenbaum is also gratefully acknowledged.

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AGGREGATED MICELLES: POSSIBLE ROLE IN GAS TRANSFERENCE

Bernard Ecanow
Reuben Balagot
Walter Stanaszek

The generally accepted hypothesis that oxygen is transferred through the aqueous media lining the lungs presents some theoretical difficulties. Oxygen, a very non-polar molecule, would thereby be diffusing through a media containing carbon dioxide and carbonates which would, perhaps critically, reduce the degree of permeability, solubility, and the rate of diffusion.[1] In addition the aqueous media would contain salts and other electrolytes which would further decrease permeability and solubility; thus, an alternative hypothesis is worth considering.

An alternative mechanism has been proposed, based on the selective solubilizing power of surfactant solutions when the surfactant molecules are in differing states of aggregation.[2,3,4] Surfactants dispersed principally as individual molecules in water give a media which absorbs little or no non-polar molecules. When a sufficient number of surfactant molecules have been added to reach a saturation point, they aggregate into units which are named micelles. At this concentration there is a sharp drop in surface tension and a rapid increase in the ability to solubilize non-polar substances. Continued addition of surfactant increases the size of the micelles and finally results in the micelles aggregating to form continuous structures.[5] Again there is an increased ability to solubilize non-polar substances.

The essence of the proposed mechanism recognizes that the respiratory system, as other systems of the body, is in a continuous state of change. Thus expansion and contraction of the surface would to some extent disaggregate the film structure and reform it. Sufficient structural change would be accompanied by a change in film solvent character

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from non-polar to polar and the reverse.

In the case of the lung expansion and contraction tension on the surfactant structure gives a polar media which permits passage of the carbon dioxide to be released in the air above the lining, and the other end of the cycle (compression) concentrates the surfactants to give a non-polar lining which can absorb non-polar physiological gases and anesthetics.

As a first test of this concept, the absorption characteristics of lung surfactant from humans and dogs were investigated. Various preparations of lung homogenate were exposed to an atmosphere of Halothane gas, and the amount of gas absorbed was measured by use of a gas chromatograph. Dilute homogenate suspension over a period of twenty minutes did not absorb any measurable amount of gas. Concentrated surfactant suspension began to absorb large quantities as soon as exposed to the non-polar gas.[3] Current research in our laboratories shows that oxygen is also readily absorbed into concentrated lung surfactant.

When lung extracts are studied on a Langmuir-Wilhelmy surface balance and the surface tension plotted against the area of expansion and contraction, a hysteresis is obtained. In attempting to elucidate the mechanism of the hysteresis, it has been reported[6] that the properties of the loop were dependent on the electrolytes in the subphase. Injection of sodium chloride into distilled water and subphase produced a lowering of the maximum and minimum surface tension values. The authors stated that this mechanism was important to the circulation of surfactant molecules from the alveolar cell to the surface film. There are theoretical difficulties with this salt-controlled mechanism. The addition of salt from a concentration of 0.15% to 1.4% gave essentially the same results. Thus, this would not be a very sensitive control mechanism. Furthermore, the salt concentration in the lung fluids probably remains within narrow limits of the normal physiological value. Also salt tends to drive lung surfactant out of solution, and once this occurs further salt addition will not change the hysteresis. Indeed further salt addition will tend to raise the surface tension values. A critical test is that other conditions change the shape of the hysteresis without changing the subphase salt concentration.[4]

Our proposed theory would explain this phenomenon on the basis that the salt lowered the solubility point (C.M.C.) of the surfactants as compared to the C.M.C. in distilled water, and therefore more surfactant was forced to the surface and lowered the surface tension.

The greater area of the loop in the salt solution as compared to distilled water indicates the presence of increased structured bodies (micelles) which require more time to reorient as the cycles proceed.

The presence of cigarette smoke on bronchial washings is known to change the hysteresis.[4] The area of the hysteresis is reduced as the maximum surface tension is reduced. In contrast to the effect of salt however, the minimum surface tension value increases with the presence of suspended particles.

We have explained these results as follows:

The insoluble colloidol-sized smoke particles adsorb and thereby concentrate the dispersed surfactant molecules. This concentration of surfactant molecules on the particle surface acts as aggregated micelles or polymolecular films; thus they lower the surface tension values of the dilute surfactant solutions, and they measurably increase the ability of these solutions to absorb non-polar gases. On the other hand, the presence of the particulate matter upon the concentrated surfactant solution interferes with the surfactant aggregates' ability to absorb gases. The adsorption of solutes from solution by insoluble particles is well known. In the cases where the adsorption of the solute is in layers greater than mono-molecular, equations such as that of Brunauer, Emmet, and Teller (the BET equation) are used to quantitatively describe the phenomena.

SUMMARY

We have investigated the ability of these adsorbed polymolecular aggregations to absorb gases. Thus dog plasma samples would not absorb trichloroethylene or ethyl ether, but when colloid insoluble particles (sulfadiazine) were dusted upon the surface, the surface tension was lowered and the adsorption of the gases began immediately and in significant amounts.

The current molecular biological investigative approaches tend to pay increasing attention to the presence of micellar aggregates.[7,8]

Biological systems are dynamic in nature, and thus structures of micellar aggregates could take different physiochemical forms each of which has unique properties.

In the case of the respiratory system it has been proposed that the alveolar lining exists in a dynamic state of compression and tension and thus either in the state of a micellar-aggregated film (non-polar) or a dispersed micellar lining (polar) when functioning properly.

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A COMPUTERIZED HOSPITAL: How? What? Why? When?

Julia T. Apter

For at least a decade some people, including physicians, have recognized that electronic computers are potentially valuable adjuncts in the management of hospital matters. Some of these people were associated with granting agencies at the United States Public Health Service, and they arranged to have all hospital-associated, computer-minded people amply subsidized to demonstrate this potential. Others were associated with computer manufacturers who dealt out (free) large, up-to-date computers. Our own west side medical center was offered an IBM 7094 system and turned it down. But California Institute of Technology, the University of California at Los Angeles, Latter Day Saints Hospitals, and others accepted and are using them ably to demonstrate the heuristic value of a large computer system in biologically oriented institutions.

Although institutions with computers are learning and teaching a great deal, the experiences of United Air Lines indicate that hospitals still have something to learn about the help available from computers. The air line has four very large, up-to-date computers with 3000 on-line terminals throughout the 50 states. The computers follow the moves of crews, planes, passengers, equipment, weather. Input is supplied and output read by secretaries, technicians, maintenance men, pilots and stewardesses. What is feasible for them should certainly be feasible for hospitals with nurses, technicians, secretaries, and physicians. It seems logical, too, that what is necessary for the speedy, safe conduct of United Air Lines is probably also necessary for hospitals.

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May I introduce you to computers simply to familiarize you with their advantages, and disadvantages. I will be neither comprehensive, nor exhaustive, but merely informative in a way that I have found computer experts to be. I will be passing on to you some facts pertinent to a hospital computer.

• *What is a computer?* Electronic computers are inanimate devices which perform mathematical and logical tasks quickly and accurately. The human brain is also a computer, a living computer. In general, but not always, electronic computers perform their tasks more quickly and more accurately than biological computers.

Electronic computers must be programmed by biological computers in order to perform at all. All information necessary for accurate performance must be stored in their memories. They get this information from experienced, knowledgeable people who know how doctors make decisions. A doctor conferring over the telephone with a nurse who is at the bedside of a patient reviews present and

previous data, computes differences and ratios, draws conclusions about trends in the patient's condition and decides on future courses of action. An electronic computer can do the same things with a nurse's report and, in some ways, can do them better than the doctor because of certain special advantages of a computer. Its memory is not fallible and can be bigger than a single human memory. Its mathematics are performed more reliably. It will not make allowances for human errors and will insist on a *complete* report of signs and symptoms more stringently than most humans. It is not only immune to superstitions like "deaths come in threes," but also to anxiety about recent failures, as well as to the influence of recent illnesses of other patients except if such illnesses are communicable. Besides these advantages, a computer, like a physician, can *learn* from a human brain which continually accrues new knowledge. New diseases, new information about a patient, responses of the patient to treatment, are all programmed back into the computer, sometimes even automatically in the "learning" computer programs.

• *What kinds of computers are there?* Electronic computers can be classified as to size, generation, type, and purpose:

Size. Small (DEC PDP-8), Medium (IBM 360/40 & 50, UNIVAC 418 III), Large (CDC 6600, IBM 360/75, UNIVAC 1108, HONEYWELL 1200).

Generation. First: vacuum tube; Second: transistorized (IBM 7094, UNIVAC 1108); Third: Integrated circuits (IBM 360/50, SDS Sigma 7); Fourth: not yet built but will include "large scale integration."

The advantage of transistorized over vacuum tube computers is a combination of smaller size, greater speed, better performance, and less "down time." The advantage of integrated circuits over the others is a combination of quicker maintenance time, much smaller sized computer, and lower cost; it does not perform better or faster and has no fewer down times; rather, it can be fixed faster.

Type. Digital; analog; hybrid (analog combined with digital). An operational distinction between analog and digital computers may be more useful to a physician than a text definition. Digital computers perform mathematical and logical tasks very fast but have to do them seriatim, or one after another. Analog computers perform some special mathematical problems, e.g., solving differential equations, even faster, and do them simultaneously or in parallel. Experts are recognizing that some biological problems may be too big ("transcomputational") for digital computers but not for analog computers. Hybrid systems are considered best for biological applications so that the speed and expandability of analog computers may be combined with logical decisions provided by digital computers. Despite the obvious advantages of hybrid systems there are very few operating at present.

Purpose. A "special purpose" computer is built (hard-wired) to perform a particular function. An analog computer built to calculate cardiac output from dye dilution curves is "special purpose." A "general purpose" computer has a wide range of applicability depending on how it is programmed. IBM systems are useful for business applications, research, or hospital information systems depending on the "soft-ware," or programs, used with the computer. "On-line" with a patient means the computer is part of the machinery receiving information and giving a display, as for patient monitoring. "In-line" refers to a bank of data stored on disks for immediate retrieval. This would be part of a hospital information system.

• *How reliable are computers?* All computers make errors. In general, however, the errors made by electronic devices are different from those made by human brains. At Massachusetts General Hospital a computer finds and corrects 100 errors a week in drug orders but makes 10 errors of its own. A human brain is required, therefore, to supervise any computer responsible for patient-care so that computer error may be recognized immediately.

Computers sometimes fail to operate, the interval until they are back in operation being called "down time." When patients depend on computers for adequate care, this down time can be dangerous. Some computers are built with this in mind. They fail with "graceful degradation"; that is, the whole computer rarely fails at once. Rather, one portion at a time fails without stopping the operation of other portions. Thus, many computers are "fail soft" with manufacturers supplying information about portions that are most hardy. Some hospitals feel it is crucial to harden this fail softness by having a second computer to take over during "down time" of a principal computer. "Fail safe" is currently taken to mean three computers; two for redundancy. When an astronaut's position in space is regulated by computers, there are more than three. The chairman of a computer committee of an 800-bed Chicago hospital claims he has 800 astronauts in space. He wants to be at least as "fail safe" as are NASA astronauts.

Eastern Air Lines has a second system for redundancy. It has been used twice in four years. Proper programming and built-in graceful degradation appear to reduce the need for a second or third computer. In general, the peripherals or mechanical devices are more likely to fail than the electronic or actual computer system.

• *Who can learn to use computers?* Some young people are designing and building computers. Others are working in the service of computers by programming them for every task the computer can possibly accomplish. These people do not conceive of a computer as service equipment so much as an object to be served. Computers, however, are amiable servants when they are large, suitably supervised, and fully programmed. It is now possible for essentially anyone to communicate with large, versatile, fast computers, as they do at United Air Lines. Cathode ray tubes offer the user an array of questions from which he may choose appropriate items and which can display answers quickly, quietly and comprehensibly. Hardware (computers themselves and their machine peripherals) have reached remarkably high levels of sophistication. Telephone companies and manufacturers of reproducing machines are keeping pace to make communication to remote places also feasible. Programs have been developed to permit a user to converse with the computer in ordinary language and receive an answer in a similarly familiar form—no matter where in the world he is.

One example of universal use of a computer by college students is given by the Dartmouth University Time-Sharing Systems. (Science, October 11, 1968.) Here they use a new language called BASIC which employs every day phrases.

Therefore, computers are for everybody: they teach children, they assist the aged and infirm, and they can reassure the retarded.

• *How long does it take to develop the Software?* Dartmouth University had its new language, BASIC, and time-sharing system in operation one and one-half months after the computers arrived, and in two and one-half months more, 11 remote terminals were in almost constant use for training. This kind of efficiency requires a group of dedicated, imaginative people. At Dartmouth, students did most of the work. Now, 80% of their liberal arts students use the computer regularly although mathematics is not a required course.

• *What are some dangers in using computers?* As already stated, people may become "addicted" and want to serve computers rather than be served by them. This phenomenon of people wanting to serve computers is well-recognized and is considered a danger evolving from exposing young people to computers too early. The reliability of computers in contrast to the vagaries of *Homo sapiens* appeals to the immature. Such people like to make the most of small computers, feel intimate with them. Students questioned at MIT about their best friend may answer "The PDP-8" or "the 3300"—and mean it. These students would rather work

with computers than do *anything*—even eat. Such persons are useful in setting up a custom-made operating system for a large computer, but must get "unhung" to be useful in putting the computer into real service.

Computers are never truly "fail safe" and must be backed up. Computers make errors and must be programmed to detect such errors or be supervised. They are expensive and become obsolescent. They (especially digital computers) may be slow in solving logical problems; they are much faster than humans in solving mathematical problems or retrieving data. This difficulty can be resolved by using (1) a "special purpose" instead of a "general purpose" computer; or (2) a suitably programmed "general purpose computer" dedicated to given tasks, such as monitoring patients or retrieving patient data. When specially built or specially programmed, the computer will be faster than if used for a variety of purposes.

Another danger is that inexperienced hospital personnel may seek advice from computer-makers concerning computer size. Strangely enough, manufacturers often suggest a computer smaller than you ask for. It makes more sense to compare a hospital's programs with those of United Air Lines or another hospital. It is also wise to keep in mind that computer programming is more expensive than the computer. Programming time will be much shorter if you acquire the computer that will be certain to remain adequately large for the longest period of time. This means acquiring the largest computer compatible with present knowledge of a hospital's needs.

• *When does a hospital need a computer for patient care?* Any hospital needs more computer power if: the pharmacists find mistakes in drug orders; computations in clinical chemistry reports are laborious; computation of radiation dosimetry cannot be done accurately in a reasonable time; rapid retrieval of patient data is crucial; post-operative patients succumb to low cardiac output syndrome before a physician can pinpoint the cause; and, in situations where physicians recognize that they did not always get around to asking for all clinical and laboratory tests indicated by a patient's signs and symptoms or did not always ask *only* for indicated tests. Such a hospital may save lives, money, and hospitalization-time with computers. Patient payment for computerized assistance in his care is readily justified, although it is not yet a reality.

• *When does a hospital need a computer for training medical personnel?* Computerized aids to medical care are certain to be adopted eventually. A hospital that trains residents and other medical personnel will want to have available training in such aids. There is, to be sure, a danger that residents trained to rely on computers will find the practice of medicine irksome in hospitals not supported with adequate computers. But, should a hospital wait until its young attending men ask for computer aids because they received training in a hospital so outfitted?

In order to communicate with a computer, the user must first learn to state his problem in unassailably logical terms. This process takes place during "computer programming." Programming is essentially a translation or teaching process, with the teacher being a knowledgeable human and the student being an efficient "moron." Teachers know that a subject must be mastered if it is to be well-taught. Therefore, programming greatly enhances a user's basic understanding of his problem. When the teacher is a resident and the student is a computer, the teacher has received a remarkable new stimulus to learning and to creative thinking because the "student" can serve the teacher so amiably and efficiently when the programming job has been successfully completed.

• *When does a hospital need computers for research?* A computer in a hospital sponsoring clinical research, even if animal research is an integral part, will be heuristic for the discovery of new, clinically useful information. A large computer on location stimulates research personnel to consider tackling problems otherwise re-

garded as impossible. Residents learning how to use an analog computer very often suggest new research problems to their teachers. Whatever research goes on in a hospital, it will be more instructive if computers are part of it because of the heuristic value of computers; they are aids to discovery.

• *What kind of computer does a hospital need?* It should be hybrid, large, specialized for hospital needs, third generation, expandable, and adequately redundant for safety.

It should be hybrid because the speed and size of the digital part of the system can be reduced if some tasks best performed with an analog computer are so performed. An analog computer is, in addition, an excellent teaching device, easy for novices to learn, and instructive in the science of "model-building." It is also well-suited for a large variety of clinical research problems since it is well adapted for "simulation" of biological systems. The digital portion of the system is best suited for management tasks and for hospital information systems.

It should be large because the responsibilities in an 800-bed hospital are numerous and must be shared by many people. United Air Lines has the same kind of problems. It uses four Univac 1108 computers with 3000 on-line terminals to monitor the locations of planes, crews, passengers, and equipment, the age of parts, etc. A hospital needs similar information about every patient now in the hospital and ever in the hospital; about drugs, blood units, equipment, personnel. One hospital executive thinks it would take one and one-half 1108's to do his job and another one and one-half 1108's to be ready to step in during "down time" with 40 on-line terminals.

It should be up-to-date (third generation) since the programming necessary to put the computer to work will be much more expensive than will be the computer itself. The computer may be expected to serve for 15 years once it has been programmed for hospital use.

For special problems such as finding radiation dosimetry, monitoring patients, research projects, there would be a variety of special purpose computers. These might be rented in anticipation of programming suitable to make some large, up-to-date general purpose computer available for those same tasks. Such projects make it necessary to put biological input into a special form suitable for a large computer. This means that aortic pressure curves for example have to be sensed by a smaller, dedicated computer which puts the curves into a set of numbers suitable for the large computer to analyze. There will also be a need for displaying to the physician the information he wants such as cardiac output, electrocardiographic diagnosis, and peripheral resistance values.

• *What kinds of computers do hospitals have now?* Most hospitals have medium or large, first or second generation computers to serve the business functions of the institution. Many hospitals have similar computers to facilitate clinical laboratory computations and dissemination of results. It is also possible to dedicate such a computer to monitoring a single patient much more thoroughly than otherwise or to perform a particular monitoring task on a large number of patients. Clinical research is also possible with small or medium-sized computers although most hospitals obtaining computers for these purposes are now getting large, third generation types. Every patient-monitor instrument that computes heart rate from an electrocardiogram contains a small special purpose computer. General purpose computers may eventually replace them. Large special purpose computers for detailing radiation controls in radiotherapy are available, but also may eventually be replaced by a larger, more general system.

When hospitals recognized during the past decade that computers belonged in the medical practice of the future, they obtained funds to demonstrate this. Some problems they worked on were abortive; others were productive. Salt Lake City hospitals, for example, are outfitted with several systems of two medium size third

generation computers for monitoring patients although some of the research projects started there have not proved successful elsewhere. Men of vision in Salt Lake City have set that city ahead with large computer systems that can be used for a great many more medical-care tasks than only on-line patient monitoring.

• *How can a hospital get funds for computerization?* These could derive from management costs, patient care income, medical personnel training grants and research grants.

The large, up-to-date computer described here probably provides more computer power than hospital administrative offices require. However, it can certainly suffice for their needs as well as for other functions. Therefore, management would do well to divert funds currently supporting a smaller computer into the new service. Patient care funds could come from Blue Cross and other health insurance agencies. When such agencies become convinced that computerization shortens hospital stays and lengthens lives, they will pay to the computer a suitable amount for each patient hospital day. If such agencies are not convinced shortly, for lack of adequate evidence, a research project to collect such evidence would be indicated. However, the air lines' experiences should be sufficiently convincing that large computers do save lives and time. Several people in Chicago who are interested in seeing hospitals computerized are currently collecting resources to justify Blue Cross payment for suitable hospital computers. By the same token, it is unlikely that Blue Cross would support computers inadequate for the job of shortening hospital stay. If they will support any computer at all, it is more likely to be the very large, redundant systems.

• *How to apply for funds to support research and training in a computerized hospital.* Some places that do have funds are willing to share their secrets for obtaining such funds with other institutions. Sometimes we just have to follow our own common sense in deciding on research projects and the necessary computer support. One new myocardial infarction research unit was supported for the purchase of a small, second generation computer. Another such unit with two medium-sized third generation computers was also supported. In both institutions the aim is eventually to provide fail-safe monitoring of patients; the funds are for research into how to accomplish this. A third institution has had support for seven years for a medium, first generation computer combined with a large, second generation computer to conduct 46 clinical research projects while a PDP-8 (small, first generation) converts clinical data into a form suitable for the large computer system. The primary accomplishment of the past year was the development of the data conversion techniques.

Suitable research projects might include new ways to program a large computer efficiently for hospital applications or to develop a hybrid system: To test a method applied successfully to animals but not yet tested in humans; to test the applicability of methods widely used in the physical sciences and promising, by analogy, to be of assistance in some clinical area; to test, rigorously, a method recommended by one reliable institution and not yet tested elsewhere. Since large hospital computer facilities seem necessary and inevitable, but are still scarce, early positive action may be profitable. Certainly the success of United Air Lines in efficiently keeping men safe, with secretaries doing most of the man-machine interaction, is encouraging. There is every reason to expect other institutions, including hospitals, to have comparable success, with secretaries, nurses, technicians and physicians conversing with computers.

It would seem reasonable not to expect funds for projects that are not research. The United States Public Health Service clearly turns such projects down. For example, if one hospital claims to compute cardiac output from aortic pressure curves, but five other institutions are

unable to repeat the methods and can show why they are unsuccessful, it might be wise not to expect such a project to be fruitful on your computer. On the other hand, a method amply used and tested elsewhere should not be referred to as a research project when applied for the first time at your hospital. It has become, instead, a valid addition to medical armamentaria.

Or, how about applying for funds to show some new ways in which a large computer can improve health services? Only a hospital with a large computer can do this kind of research. Much other research could be performed with only a small portion of the large computer, even though the larger computer simply made programming simpler and had more heuristic value than the smaller one.

• *Realities.* After a hospital acquires a computer, it needs a proper atmosphere to retain the programmers and systems analysts necessary to put the computer into action. Even then, it takes a long time before the computer is performing optimally. It would be ill-advised to attempt to computerize a whole hospital at once; better to start by providing thorough service to one area of the hospital or to one crucial department, like radiology. While working to make the performance of the system as diversified and encompassing as possible, the programmers will become impressed with the vast amount of information stored in a patient's chart and in his physician's memory. The job is far from trivial; but the job to be accomplished performs a far from trivial function. Suffice it to say that some hospitals already have systems for retrieving at will over 100 pieces of information obtained every 10 minutes on a single patient in intensive therapy. Such success makes it obvious that a group of 10 patients or of 1000 patients can be monitored similarly, if necessary, with adequate computer power.

It has not proved realistic to expect outside computer experts to computerize a hospital. Few such experts seem to be oriented to putting computers to work *for* people. One large community hospital spent five million dollars having bright young engineers develop programs to interview psychiatric patients, to teach computers how to program themselves, to find doctors' errors in drug orders, and to retrieve certain basic information about patients. Only the last two projects were truly hospital-oriented and are still being used. The other programs interest computer technologists but were not properly developed with hospital funds.

SUMMARY

The length of patient stay in large hospitals is prolonged because retrieving and disseminating information is currently a slow process. Computers are tools which can simplify, fortify and speed up hospital care of patients. Large digital combined with analog computers to form a hybrid system are best for this purpose and are successfully used by industry and the federal government. Hospitals have special problems because the necessary information about each patient is enormous and time is of the essence. However, the state of computer art is ready for the problems. A computer large enough to solve hospital information problems will also be large enough for sophisticated research and in-depth training of all medical personnel. Shorter hospital stay suggests that patients could pay for computer service; research and training facilities suggest that public agencies could also pay. However, funding is the largest obstacle to adequate hospital computerization.

GLOSSARY

Software:—Programs
Hardware:—Equipment
Computer generation:—
  Hardware:—
    First:—Vacuum tube
    Second:—Transistorized
    Third:—Integrated circuits
    Fourth:—Large scale integration
  Software:—
    First:—Machine language
    Second:—Fortran, Algol
    Third:—Operating system
Transcomputational:—problems too large for any computer presently conceivable
Peripherals:—Typewriters, card-punch machines, printers, displays, light-pen
Debugging:—error correction
Heuristic:—helping to discover or learn; a method of observation in which the pupil is trained to find out things for himself
Down time:—when the computer will not work
SDS:—Scientific Data Systems
CDC:—Control Data Corporation
DEC:—Digital Equipment Corporation
EAI:—Electronic Associates Inc.
Univac:—Sperry-Rand Corporation

SUGGESTED READING

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THE FAMILY PLANNING SERVICE

Arthur H. Klawans
Joyce C. Mayer

The Family Planning Clinic of the Health Center of the Presbyterian-St. Luke's Hospital has been operating in its present format for two years. This program can now be considered successful. In a recently published article[1] we described in detail the development of this clinic and set forth eleven innovations which were unique to this operation and which could provide guidelines for any hospital wishing to initiate a similar program.

On July 1, 1966 the then-existing Family Planning program was revamped. The revised plan had as its backbone the replacement of highly trained professionals by volunteers. Many of the areas previously considered sacrosanct territory of the physician, the registered nurse, or the licensed practical nurse (LPN) were efficiently and satisfactorily handled by properly trained and motivated volunteer workers. Our results speak for the wisdom of this move.

With a staff consisting of two supervising staff physicians, two volunteer physicians, and seven volunteers we are able to conduct three clinic sessions a week. There is a twice-weekly presentation in the post-partum wards of the hospital, at which all available methods of contraception are displayed and explained by the volunteers. After this presentation, patients are encouraged to ask questions either in open forum or in personal confrontation. Any questions the volunteer cannot answer are referred to the physician. The participation of any patient in the program is entirely voluntary and the choice of method is left to the patient unless medical indications dictate otherwise. Appointments are then given for the patient's return to the Post-Partum Family Planning Clinic six weeks later.

At the post-partum session in the clinic patients are examined by the attending physician. If, at this time, there are no contraindications, the method of choice is applied as of that day. Specially prepared flow sheet records are kept on each patient and retained in the clinic for quick reference and statistical recapitulation. These records were devised with the aid of the volunteers and are maintained by them.

All patients requesting oral contraception meet in a class conducted by a volunteer who outlines the procedure for use of the medication and supplies each woman with a personal calendar marked to show 'days on" and "days off" the pills. Any questions regarding the oral contraceptive regimen, or the effects of the drugs, which cannot be answered by the volunteer are referred to the physician.

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Because most of the explanatory pamphlets accompanying the oral contraceptives as prepared by the pharmaceutical companies manufacturing these products are aimed at middle class audiences, we felt that these were not suitable for our clinic clientele. A special brochure designed to meet the needs of our patients was prepared by the authors in cooperation with other volunteers and the hospital Public Relations Department, A copy of this brochure is provided each patient following the class instruction period.

If the patient requests an intrauterine contraceptive device (IUCD) this is inserted by the attending physician at this time. If the diaphragm is desired, it is fitted and the patient is instructed in its use by a demonstration to insure proper usage. If contraceptive foam is to be used the volunteer explains the proper application of this product.

All supplies not paid for by public aid agencies are provided through a generous grant from the Womans' Board of the hospital. The original cost of the preparation of the oral contraception brochure and printing of the first 1,000 was defrayed by a special grant from the Womans' Board to the Health Center.

Patients who elect to use oral contraception are given a prescription for three cycles of pills and are given an appointment to return in two and one-half months. At this time it is determined whether there are any side effects from the medication; the breasts are checked to be certain that no cystic formation is developing. Then, if all is in order, these patients return at six-month intervals for examination and prescription refills.

Patients who have IUCD insertions return in one month to be examined for proper retention of the device and to determine whether there are untoward effects. If all is in order, they return at six-month intervals for pelvic examination. Women using diaphragms or contraceptive foam are examined every six months.

Cytological testing is performed on all patients at yearly intervals.

RESULTS:

Eight-hundred, fifty-five patients enrolled in the newly organized Family Planning Service during the first year of operation. Since the advent of the Mile Square Health Center about 25% of our hospitalized obstetrical patients are registered through that facility and return there for post-natal and family planning services. During the first year of the Mile Square operation 642 Family Planning patients were cared for at that Center. In spite of this, our total Family Planning Clinic load in the hospital Health Center for the two-year period reached 1901 patients, an increment of 1046 during the second year. Considering that these patients are primarily recruited from those delivered at the hospital and that they are attracted to our service from all parts of the city, we regard this as an amazingly gratifying number and a tribute to the services rendered at all levels of our effort.

An analysis of the contraceptive methods chosen by the patients after proper indoctrination is as follows:

Oral contraception	1138
Intrauterine devices	656
Diaphragm	83
Foam	23
Condom	1
Total	1901

Following our previously described routine for return visits there were 3403 such visits, with a grand total of all clinic visits of 5304, distributed as follows:

Method	Original Visits	Return Visits	Totals
Oral	1138	1592	2730
IUCD	656	1756	2412
Diaphragm	83	46	129
Foam	23	8	31
Condom	1	1	2
Totals	1981	3403	5304

In all significant reports in the literature from family planning services throughout the country the failure rates are of consequence. In our first year of operation we showed a "dropout" rate on oral contraception of 18%. This com-

pared favorably with a 25% rate[2] in the clinics of the Chicago Health Department. In general, 30% is considered as a respectable "dropout" rate.[3] Our two year "dropout" rate has reached this latter level, a figure with which we are not particularly pleased but which has several possible explanations.

No patient who continued to take pills according to our instructions has become pregnant.

Failures with the use of intrauterine devices are classified as follows:

Spontaneous Expulsion.....	37	5.6%
Removal for cause		
Pain, bleeding, desire for pregnancy, etc.....	80	12.3%
Pregnancy.....	10	1.5%
With IUD in place.....	3	
With IUD out of place...	7	
Severe infection.....	5	0.7%
Total.....		20.1%

This total compares favorably with other reports on much larger numbers of patients most of which run to about 25% failure.[4] Our removal rate is quite high and throws our over-all figure off because of an inordinate number of removals done by several persons associated with the program in the past who were opposed to this method of contraception.

As far as we can determine, no patient using the diaphragm or foam has become pregnant while applying these according to instructions.

It is evident from the figures presented above that the Family Planning Service has been a success. This unique program, with its many innovations, has made a substantial contribution to the welfare of the community.

SUMMARY

The Family Planning clinic of the Health Center has operated with volunteer help since July 1, 1966. All contraceptive pills and intrauterine contraceptive devices provided the predominant methods used. Figures are presented illustrating the general success of the clinic which has employed several innovations in its organization.

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ABSTRACTS AND REVIEWS

OF PUBLICATION BY THE STAFF

Scheving, L. E.; Harrison, W. H.; Gordon, P.; and Pauly, J. E.: Daily Fluctuation (Circadian and Ultradian) in Biogenic Amines of the Rat Brain. *Amer. J. Physiol., 214: 166-173, Jan. 1968.*

Fluorometric measurements were made of serotonin, dopamine, and norepinephrine extracted from brains which were obtained from different subgroups of adult male rats killed at hourly intervals over three separate 24-hr. periods. With a method involving sampling at hourly intervals, a synchronized circadian rhythm in serotonin with a crest extending from 1130 to 1730, followed by a trough between 2030 and 2130 was demonstrated in rats maintained on a 12-hr. photoperiod (0600 to 1800 CST) followed by 12 hrs. of darkness. Although a circadian rhythm was not detected for dopamine and norepinephrine in the whole brain, the data did suggest that these two catecholamines are characterized by reproducible higher frequency, ultradian rhythms. The importance of these studies involving the biogenic amines, their specific relationship to the physiology of sleep, and their pertinence to neurochemical studies are discussed.

Harrison, W. H.; Whisler, Walter W.; and Hill B. J.: Catecholamine Oxidation and Ionization Properties Indicated from the H^+ Release, Tritium Exchange, and Spectral Changes Which Occur during Ferricyanide Oxidation. *Biochemistry, 7: 3089, 1968.*

Oxidations by ferricyanide ion of compounds with dihydroxyphenylethylamine structures to indole derivatives were studied by measurement of the H^+ release and spectral changes which occur in reactions maintained at constant pH by a pH-Stat technique. The results were verified in the case of adrenaline by measurement of the ^3H release accompanying oxidation of H-ring-labeled adrenaline. The catecholamines and related compounds studied included adrenaline, noradrenaline, dopamine, α-methyladrenaline, α-methylnoradrenaline, dopa, epinine, adrenalone, noradrenalone, and isoproterenol. Their oxidation at pH 7 was found in each case to involve reduction of 4 equiv of ferricyanide (transfer of four electrons) and the release of 5 equiv of H^+, indicating formation of the aminochrome derivative. The stoichiometry indicated that release of 4 H^+ equiv resulted from the oxidation; the additional H^+ equivalent released reflects the protonation of the side-chain amino nitrogen atom which most probably is converted in the cyclization step into an imino nitrogen which has negligible affinity for H^+ at pH 7. Studies of oxidations of adrenaline, noradrenaline, and dopamine at pH <7 indicated that the oxidations proceed to the aminochrome stage but, however, are incomplete; in the presence of Zn^{2+}, the reactions proceed to a further extent, being complete down to pH 4 for noradrenaline and dopamine and to pH 3 for adrenaline. The method described should prove useful for the direct determination of the extent of protonation of other compounds of this type.

Klawans, Harold L., Jr.: Delayed Traumatic Syringomyelia. *Dis. Nerv. Syst., 29: 525-528, Aug. 1968.*

A case of progressive myelopathy becoming clinically evident 14 years after the onset of traumatic paraplegia was reported. The pathologic material clearly demonstrated that the neurologic deficit was related to an extensive syringomyelia which extended from the level of the scar up to the medulla oblongata and that the syringomyelia itself was pathogenetically related to the previous trauma.

Lashof, Joyce C.: Medical Care in the Urban Center. *Ann. Intern. Med., 68: 242, Jan. 1968.*

The problem of providing medical care in the urban center is analyzed from the point of view of distribution of health manpower, costs of medical care and organization of services. The dual system of medical care which leaves the urban poor dependent on a multitude of fragmented services without continuity is described. The development of neighborhood health centers is offered as one solution to the problem.

Lepper, Mark H.; Lashof, Joyce C.; Pisani, Albert; and Shannon, Iris: An Approach to Reconciling the Poor and the System. *Inquiry, 5: 37-42, Mar. 1968.*

We have presented the story of a comprehensive care program which has been developed under the auspices of an urban university-affiliated teaching hospital utilizing OEO funds that was designed to meet the needs of primary phases of care, but with assured hospital backup. As new problems are recognized, new approaches will be attempted. The areas of social and psychologic factors are indicated as those needing most effort at this time.

Lashof, Joyce C.: The Health Care Team in the Mile Square Area, Chicago. *Bull. NY Acad. Med., 44:1363-1369, Nov. 1968.*

The organization of the Mile Square Health Center of Presbyterian-St. Luke's Hospital is described. Services are organized around three echelons of care: the public health nurse and community health aids, functioning in the home and community; the neighborhood health center providing general office care; and the hospital providing specialty services and in-patient care.

The composition and functioning of multi-discipline health care teams is presented.

Klawans, Arthur H.; Kilbourne, B. A.; and Mayer, Joyce C.: Family Planning Service In A Voluntary Hospital. *J. Reprod. Med., 1:449-455, 1968.*

Although the innovations developed in the course of our program are stated, it is felt that we should list them here as a guide for those who consider the institution of a similar service.

1. Funding with privately donated funds. The majority of hospital women's boards are searching for worthwhile projects. No area of patient care has a greater appeal to women than that of family planning.
2. The use of volunteer obstetrician-gynecologists to conduct the examinations, prescribe the proper method for each patient and carry out the application of the physical devices. This provides a safer and more satisfactory care than is provided in programs conducted by less experienced personnel.
3. The use of volunteer workers to carry out duties usually delegated to highly paid professionals for patient recruitment, patient teaching and record keeping. Careful choice of volunteer workers results in an efficient operation without cost.
4. The application of the chosen method of contraception at the time of the postpartum menstrual period.
5. The oral contraceptive cycle to be started one week from the date of ingestion of the last pill of the previous set. This eliminates the confusion that may be produced by aberrance in the withdrawal bleeding picture.
6. Providing services to all interested patients without coercion or regard to age, religion or marital status. The only criterion for admission to the program is a previous pregnancy.
7. The use of vaginal foam as a stop gap between the time of leaving the hospital and the time of the postpartum examination in patients uncertain of their ability to practice continence during this period.
8. The use of a specially devised calendar, individually prepared, for the guidance and reference of patients using oral contraceptives.
9. The use of a specially prepared booklet explaining the use of oral contraceptives in a manner understandable to the clientele served.
10. The use of a special reference sheet for each patient, separate from the Health Center

record, which is retained in the clinic for quick reference and purposes of statistical recapitulation.

11. A triple exposure to the advisability and desirability of Family Planning Services and supplies presented by the same personnel at all levels. This makes for a continuity of care unusual in clinic practice and appealing to patients.

Hyde, John S. and Swarts, Charles L.: Effect of an Exercise Program on the Perennially Asthmatic Child. *Amer. J. Dis. Child., 116: 383-396, Oct. 1968.*

Children with perennial asthma are difficult to manage. They require frequent antiasthma medications, often around the clock, and sometimes adrenocortical steroids are necessary. The disease is characterized by exertional dyspnea which limits their activities.

Ventilatory function findings were evaluated in 36 children with perennial asthma who attended physical fitness and breathing exercise classes one hour a week. Moderate to marked obstruction remained unchanged in 50.6% of study periods of three to four months' duration. The conditions of 9.6% of the children improved, and the conditions of 13.3% worsened. When observed over two successive terms, six to eight months, 35.3% of the patients continued to have moderate to marked obstruction, 23.5% improved, and 26.5% worsened.

These exercises do not eliminate the disease but surprisingly, by controlled breathing and relaxation, some patients breathe more efficiently. They participate in more school gymnastics and are able to cope with extra physical demands.

A complete therapeutic program for perennial asthma should include medical therapy plus special exercises to improve the patient's physical capabilities. Because the obstructive process may continue for months to years, extensive treatment is usually required for the duration.

Sutter, Richard P. and Rafelson, Max E., Jr.: Separation of β-Factor Synthesis from Stimulated β-Carotene Synthesis in Mated Cultures of *Blakeslea trispora. J. Bact., 95: 426-432, Feb. 1968.*

Mated cultures of *Blakeslea trispora*, grown in a potato extract-glucose-thiamine medium, produced 10 to 15 times more β-carotene than either unmated culture. Mated, but not unmated, cultures produced a family of compounds (β factor) which stimulated carotenogenesis in unmated cultures. In fact, carotenogenesis was stimulated sixfold more in minus cultures than in plus cultures. By altering the relative amounts of plus and minus inocula used in fermentations of mated cultures, it was possible to separate the synthesis of β factor from the synthesis of extra β-carotene. The plus strain appeared to produce the β factor; the minus strain appeared to produce most of the extra β-carotene. Kinetic studies of β-factor formation suggested that physical contact between the two strains may be required to initiate β-factor synthesis.

Halper, I. S.: Psychotropic Drugs. *Ill. Med. J., 133: 37, Jan. 1968.*

The place of psychotropic drugs in psychiatry is reviewed. It is suggested that drugs be prescribed in collaboration with the patient and that the physician be aware of underlying problems even though they are not explored with the patient. In the section on antidepressants, the place of hospitalization and electroconvulsive therapy in the treatment of depression is discussed. Recommendations are made about drugs in the case of the suicidal patient. Included in this review are sections on drugs for psychosis, drugs for anxiety, antidepressants, psychotomimetic drugs, and hypnotics.

Lepper, Mark H.: Potential Interactions between Multiple Etiologies and Pathogenesis of Experimental Diseases. *Yale J. Biol. Med., 40: 541-549, Apr.-June 1968.*

Interpretation of the action of more than one agent is considerably more difficult than that

of a single agent. Careful attention to dose-effect curves for each agent and analysis of influences of time relationships between administration can allow inferences about mechanism which might give clues to etiologic and pathogenic mechanisms in human disease.

Carnow, Bertram W. and Lepper, Mark H.: Health Effects of Air and Water Pollution. *Industr. Med. Surg., 37: 281-284, Apr. 1968.*

The air and water are able to decontaminate themselves up to a certain pollutant dose rate level. Beyond that point the cleansing mechanisms break down. In order for man to survive he must determine those levels of contamination at which the most susceptible organisms are seriously affected and, based on these levels, must set standards reflecting acceptable pollutant levels. Further studies are needed to elucidate more precisely the mechanism of action of these pollutants particularly with regard to long term effects on health. The continued rate at which the population has increased, the development of high population densities and the massive expansion of industrial production and consumption make these efforts mandatory.

Muenster, Joseph J. and Graettinger, John S.: Chest Pain in the Surgical Patient. *Med. Clin. N. Amer., 52: 91-101, Jan. 1968.*

The most serious causes for pain in the chest in the surgical patient are myocardial infarction and pulmonary embolism. Pulmonary infarction will manifest itself with a pleuritic pain, but pulmonary embolism without infarction may be clinically identical to myocardial infarction. A careful medical history prior to operation and a thorough clinical and laboratory evaluation will often serve a useful purpose in the discovery and diagnosis of postoperative complications. Serial study and observation after the occurrence of the postoperative complication may be necessary.

Miller, Paul H. and Carleton, Richard A.: Hemodynamic Assessment during Atrial Fibrillation. *Amer. J. Cardiol., 22: 568-571, Oct. 1968.*

A technic to simplify hemodynamic evaluation during atrial fibrillation by right ventricular pacing is described. The hemodynamic data obtained at cardiac catheterization during atrial fibrillation with and without right ventricular pacing were compared in three cases. Evaluation of data is simplified and valvular gradients can be measured with greater precision when the wide variability in duration of cardiac cycle and intracardiac pressures usually present during atrial fibrillation are abolished by ventricular pacing.

Chertow, Bruce S.; Hertko, Leonard J.; and Carleton, Richard A.: Pulmonary Artery Stenosis Murmurs. A New Diagnostic Sign of Pulmonary Embolism. *Arch. Int. Med., 121: 97-100, Jan. 1968.*

Massive pulmonary thromboembolism was seen in a 52-year-old Negro woman. The patient presented as a neurological problem. The occurrence of the typical murmur of pulmonary artery stenosis led to the diagnosis. Angiograms revealed almost complete resolution of pulmonary emboli at 25 days.

Ryan, Will C.; Nibbe, Albert F.; Schwartz, Theodore B.; and Ray, Robert D.: Fibrous Dysplasia of Bone with Vitamin D Resistant Rickets: A Case Study. *Metabolism, 17: 988-998, Nov. 1968.*

A patient with the unusual combination of fibrous dysplasia of bone and Vitamin D resistant rickets is described. Studies performed provide evidence for normal gastrointestinal absorption of calcium, low renal tubular maximum of phosphate reabsorption (TmP), and elevated phosphate clearance responsive to alterations in serum calcium level. Possible mechanisms underlying these disorders are discussed.

Buchner, B. K.; Sinclair, J. C.; Holmes, A. W.; and Deinhardt, F.: Studies to Identify Tissue Culture Isolates from Patients with Infectious Hepatitis. *Canad. J Public Health, 59: 399-404, 1968.*

The TF isolate has been shown to be an ECHO virus, Type 19, and is felt to be causally unrelated to the infectious hepatitis illness. The isolates CB, ML and KV, obtained from patients in a single epidemic have been identified as being antigenically related, but not identical to, Coxsackie viruses A13 and A18. Etiological relationship to infectious hepatitis has not been proven; such virus isolation could indicate a commensal or concurrent illness.

The DD isolate, obtained from a patient in a hospital outbreak of infectious hepatitis remains unidentified but has the properties of a picornavirus.

Bentley, David W.; Haque, Riaz-Ul; Murphy, Richard A.; and Lepper, Mark H.: Biotyping, an Epidemiological Tool for Coagulasenegative Staphylococci. *Antimicrob. Agents Chemother., 1967, pp. 54-59.*

A multiple inoculating device and several biochemical tests have been used in the designing of a new rapid and convenient typing system for strain classification of coagulase-negative staphylococci from clinical material. In initial determinations based on the oxidation of the sugars galactose, maltose, lactose, and mannitol, and on the detection of the enzymes deoxyribonuclease, lipase, and milk and egg yolk factors, 43 biotypes were identified from 185 specimens. Because of the number of biotypes representing a single culture (60%) and the uncertain interpretation of weak reactions, further evaluation of the tests employed seemed desirable. Accordingly, a replicating study was set up to determine the degree of variability of the original eight coded tests plus three additional ones: phosphatase, glucuronidase, and gelatinase were much more stable than the other tests, and the others were discarded from further typing patterns. When the 185 cultures were recoded, 22 biotypes were noted. Nine major biotypes accounted for 90% of the cultures examined. Two cases of suspected endocarditis were evaluated with the biotype system. Mixed biotypes were noted in the blood cultures from the patient proven not to have endocarditis, whereas a single biotype was found in all cultures from the proven case.

Ream, Norman W.; Perlia, Charles P.; Wolter, Janet; and Taylor, Samuel G.: Mithramycin Therapy in Disseminated Germinal Testicular Cancer. *J.A.M.A., 204: 1030-1036, June 1968.*

Mithramycin, an antibiotic, was used in the treatment of 30 patients with disseminated germinal testicular cancer. The antitumor effect of mithramycin was evaluable in 26. Nine patients experienced an objective antitumor response, which has been complete in two. The major responses occurred in patients with embryonal carcinoma with pulmonary metastases. No significant response was observed in patients with advanced retroperitoneal or hepatic metastases from embryonal carcinoma or in the six patients with teratocarcinoma. The toxicity of mithramycin encountered in this investigation does not preclude employing this agent as a primary treatment of metastases from embryonal carcinoma of the testis.

Long, Don M.; Bodenheimer, Thomas S.; Hartmann, J. Francis; and Klatzo, Igor: Ultrastructural Features of the Shark Brain. *Amer. J. Anat., 122: 2, Mar. 1968.*

The ultrastructural characteristics of elasmobranch central nervous system have not been previously reported. This study presents a general assessment of aldehyde perfused brain and spinal cord in three species of shark: tiger, hammerhead and Atlantic nurse. The same distinct cell types are present in the shark that exist in mammals, and similar criteria may be used for their differentiation. Neurons have frequently round nuclei with a prominent nucleoli: cytoplasm is abundant and filled with formed elements; somatic synapses and subsurface cisterns are rare. Astrocytes are smaller, and have less cytoplasm and slightly fewer organelles. Glial fibrils occur, but are not invariably present. Separating astrocytes from neurons is the most difficult identification problem. Oligodendrogliocytes are smaller,

and have denser cytoplasm and a dark nucleus. The striking feature of capillary morphology is the presence of an appreciable perivascular space containing collagen; many tortuous evaginations of this space occur into surrounding glial processes which completely invest the capillaries. Astrocyte cell bodies frequently lie immediately next to vessels, and capillaries are occasionally totally surrounded by a single astrocyte process, thus being endocellular. Smaller pericapillary processes may be either astrocytic or ependymal. Dendrites, synapses, axons, and myelin have no obvious special characteristics. Sodium, visualized by precipitation techniques, is prominent in the astroglia and neurons.

Thiele, K. G.; and Mattenheimer, H.: The Isoenzymes of Lactate Dehydrogenase in the Nephron of the Healthy Human Kidney. *Z. Klin. Chem., 6: 132, 1968.*

Isoenzyme patterns of LDH have been determined in micro dissected anatomical and functional units of the nephron of the healthy human kidney. In glomeruli the activities of LDH-2 and LDH-5 were low, while the other fractions were considerably more and about equally active. In convoluted tubules and medullary rays LDH-1 was the most active fraction, followed by LDH-2. There was little activity of LDH-3 and almost no activity of LDH-4 and LDH-5. Towards the papilla the activity of LDH-1 and LDH-2 decreased, while LDH-3 and LDH-4 became increasingly prominent. LDH-5 also increased, but the highest single value in the very tip of the papilla was only 19% of the total LDH activity.

There is no strict relation between the LDH-isoenzyme patterns and the type of metabolism, respiratory or glycolytic, in the human kidney.

The overall low percentage of LDH-5 in the human kidney is remarkable, and makes it difficult to understand the results of other authors who found that in certain kidney diseases the activity of LDH-5, which they believe to originate from the kidney, is increased in serum.

Wilson, D. M.; and Schwartz, F. D.: In vivo Incorporation of Iodopyracet into Erythrocytes of Healthy and Azotemic Patients. *J. Lab. Clin. Med., 72: 951, 1968.*

The renal tubular transport of iodopyracet (Diodrast) is altered in the azotemic individual. It is not certain whether this is due to shunting of blood from active secretory sites or due to an alteration of the transport process itself. Since the transport of Diodrast is not unique to the proximal renal tubule, we examined the incorporation of Diodrast into erythrocytes to establish whether it might serve as a model for the study of the transport process, kinetics, metabolic requirements, and control mechanisms. Accordingly, the in vivo incorporation of Diodrast was determined in the erythrocytes of azotemic and nonazotemic individuals. We report here the observation that in vivo Diodrast does not come to equal concentration in plasma and red cell water. The findings suggest that azotemia interferes with incorporation into the cell, while there is also evidence of probable active transport of Diodrast out of the red cell. The alteration in azotemia appears to be related to an extracorpuscular factor present in azotemia but is independent of pH or anemia per se. The red cell may well offer a model for the study of Diodrast transport.

Pillay, Veerasamy K. C.; Wilson, David M.; Ing, Todd S.; and Kark, Robert M.: Fungus Infection in Steroid-Treated Systemic Lupus Erythematosus. *J.A.M.A., 204: 261-265, July, 1968.*

Fungus infection occurred in 12 steroid-treated patients with systemic lupus erythematosus. *Candida albicans* was the fungus most commonly isolated. Disseminated infection occurred in four patients, and fungus infection contributed to the death of eight. The clinical characteristics of fungus infection include pulmonary symptoms, pyrexia, and progressive deterioration in the clinical state of the patient. Early diagnosis is dependent on persistent search for the infecting fungi. Predisposing factors include the underlying disease, uremia, superficial wounds, and the use of antibiotics, steroids, and immunosuppressive agents. Prevention is dependent on judicious use of antibiotics, vigorous treatment of wounds, and cautious use of steroids.

Pillay, Veerasamy K. G.; Schwartz, Franklin D.; and Kark, Robert M.: Proteinuria In Malignant Hypertension. *Lancet, 7581:1263, Dec. 14, 1968.*

Proteinuria was investigated in 28 patients with malignant hypertension. All had proteinuria at some time during the course of their disease. There was a wide variation in the degree of proteinuria. Severe, persistent hypertension with progressive deterioration in renal function is commonly associated with massive proteinuria. Control of blood-pressure is associated with a decrease of proteinuria. In 2 patients the nephrotic syndrome developed. The rarity of the nephrotic syndrome in malignant hypertension may be due to daily fluctuation and absence of persistent massive proteinuria.

Kark, Robert M.: Renal Biopsy. *J.A.M.A., 205: 220-226, July, 1968.*

The accomplishments of renal biopsy have been reviewed by Roland and Dimond who state that, in the short space of 15 years, it has made contributions to the diagnosis, treatment, and management of patients ill with renal disorders. It has illuminated the anatomy, pathology, and biochemistry of the kidney in health and disease, and it has broadened our understanding of pathophysiology, pathogenesis, and prognosis.

Most nephrologists agree that, at present, the patient is best served if renal biopsy is done in a center devoted to such work. The patient gains when the whole of his clinical history and the biopsy findings are reviewed jointly by an internist who knows a great deal about renal histology and a specially trained pathologist who knows something about clinical nephrology and urology. We believe, however, that the pattern of practice is changing. In the future, many biopsies wil be done in community hospitals with appropriate consultation in medical centers. The technique of renal biopsy can be learned by any doctor who is not ham-handed, but if he wants to do renal biopsies, he should be trained in nephrology at an appropriate center. When he returns to his own hospital, he should have the opportunity to do biopsies regularly, otherwise he will lose his technical skill and his nephrologic judgement. The casual biopsy on the occasional patient leads to nothing but harm.

RESBYTERIAN-ST. LUKE'S HOSPITAL MEDICAL BULLETIN